SYNTHESIS OF POTENTIAL ANTHELMINTICS

(SUMMARY)

A THESIS SUBMITTED FOR THE DEGREE OF

Doctor of Philosophy

IN

Chemistry

TO

THE ALIGARH MUSLIM UNIVERSITY, ALIGARH

BY

SYED ABUZAR

M. Phil.

DIVISION OF MEDICINAL CHEMISTRY
CENTRAL DRUG RESEARCH INSTITUTE
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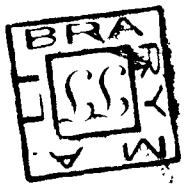

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S U M M A R Y

The survey of world-wide incidence of various helminth infestations in man which appeared time to time reveals that despite several measures taken to eradicate helminth infections its growing trend has not been checked[1]. Although helminth infections are not generally fatal, they contribute to the major public health problems in tropical and subtropical regions of the world[2,3] and may also lead to several clinical complications causing even death of the patient in absence of immediate medical care. The high prevalence of helminth infections is partly due to the poor sanitary habits and lack of prophylaxis followed by masses, abundance of proper natural conditions for the developments of helminth juveniles and partly due to the lack of suitable drugs available for the treatment of different forms of helminthiasis. The present thesis is an effort to develop ideal chemotherapeutic agents for the treatment of infections due to hookworms and cestodes, the two major helminth diseases of tropics.

The efforts to substitute classical anthelmintics by more effective and safer drugs was unsuccessful till 1961 when Merck came out with the discovery of thiabendazole[4], a new class of anthelmintic possessing broad spectrum of activity against a variety of nematode parasites in man and domestic animals. This led to the discovery of a series

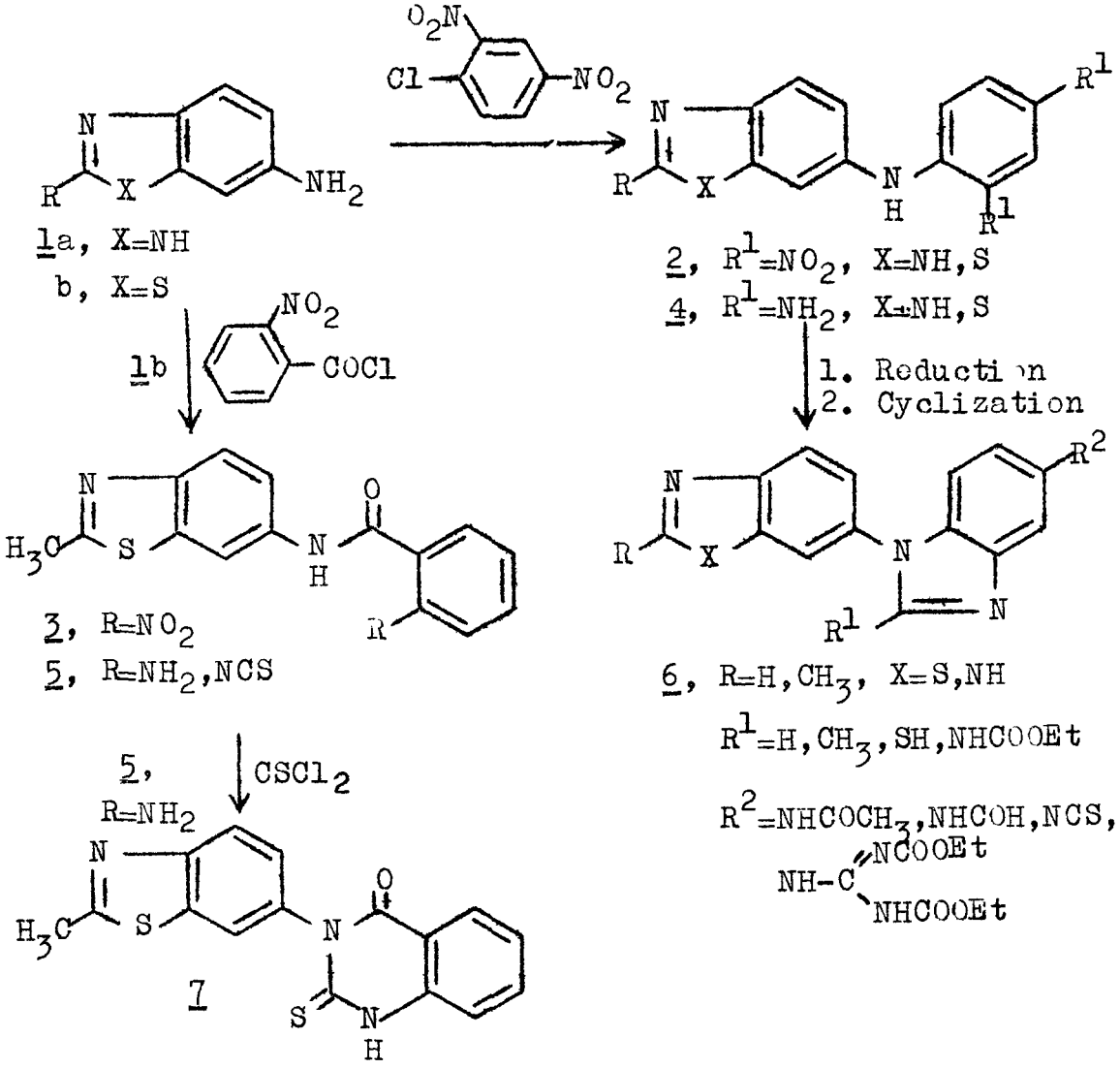
of potent benzimidazole anthelmintics of which mebendazole[4] and fenbendazole[4] showed high promise in curing nematode and cestode infestations and also established benzimidazole heterocycle as a useful pharmacophore for building molecules with broad spectrum of antiparasitic activity.

The first chapter of the thesis presents a review dealing with the recent developments in the treatment of hookworm and cestode infections. The second chapter comprises of the synthesis and biological activity of the different classes of the compounds based on the powerful anthelmintic activity associated with benzimidazoles[5], diaryl sulfides and sulfones[6] and bitoscanate[7]. This study has been carried out with a view to develop better anthelmintics as also to delineate minimal structural requirements for optimal anthelmintic activity in the molecular frame-work exhibited by the 'lead' molecules.

Synthesis of 5(6)-N-heteroarylbenzimidazoles and benzthiazoles

Several 5(6)-(1-benzimidazolyl)benzimidazoles and 6-(1-benzimidazolyl)benzthiazoles (6) have been prepared starting with the condensation of 5(6)-aminobenzimidazoles (1a) and 6-aminobenzthiazoles (1b) with 2,4-dinitrochlorobenzene or 2-nitrobenzoylchloride to give 5(6)-(2,4-dinitrophenyl)aminobenzimidazoles and benzthiazoles (2)

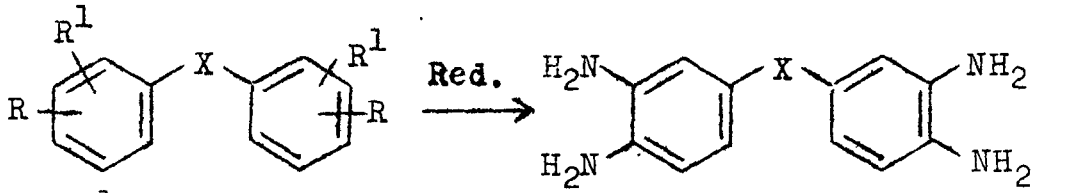
and 6-(2-nitrobenzoyl)aminobenzthiazole (3) respectively. Reduction of 2 and 3 with Raney-nickel and H_2 or hydrazine-hydrate and Raney-nickel gave the corresponding amines (4 and 5) which were cyclized with different cyclizing agents to give the title products (6 and 7)[8,9].



Synthesis of 2,2'-disubstituted-5,5'-dibenzimidazolyl derivatives

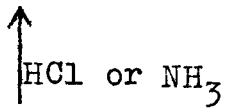
Based on the powerful anthelmintic activity associated with benzimidazoles[5], several 2,2'-disubstituted-5,5'-dibenzimidazolyl derivatives (11) have been prepared in order to study the role of benzimidazole moiety as a

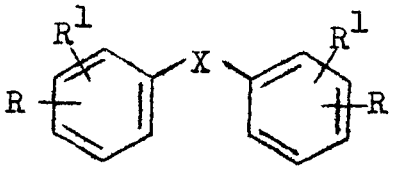
carrier molecule. The key intermediates in the synthesis of above compounds were 3,3'-dinitro (or diamino)-4,4'-diamino (or dinitro)diphenyl derivatives (9) obtained either by hydrolysis of 4,4'-diacetamido-3,3'-dinitro diphenyl derivatives (8a) or by amination of 4,4'-dichloro-3,3'-dinitrodiphenyl derivatives (8b) or by direct reaction of 5-chloro-2-nitroacetanilide with sodium sulfide. Reduction of 8 with hydrazine-hydrate and Raney-nickel, Raney-nickel and H_2 or ferrous sulphate-ammonia gave the corresponding 3,3',4,4'-tetra-aminodiphenyl derivatives (10). Reaction of 10 with 1,3-dicarbalkoxy-S-methylisothioureas, acetic acid or formic acid yielded the title compounds 11.



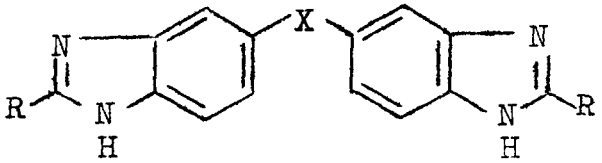
9, R^1 = 3-NH_2 or 3-NO_2
R = 4-NH_2 or 4-NO_2

10





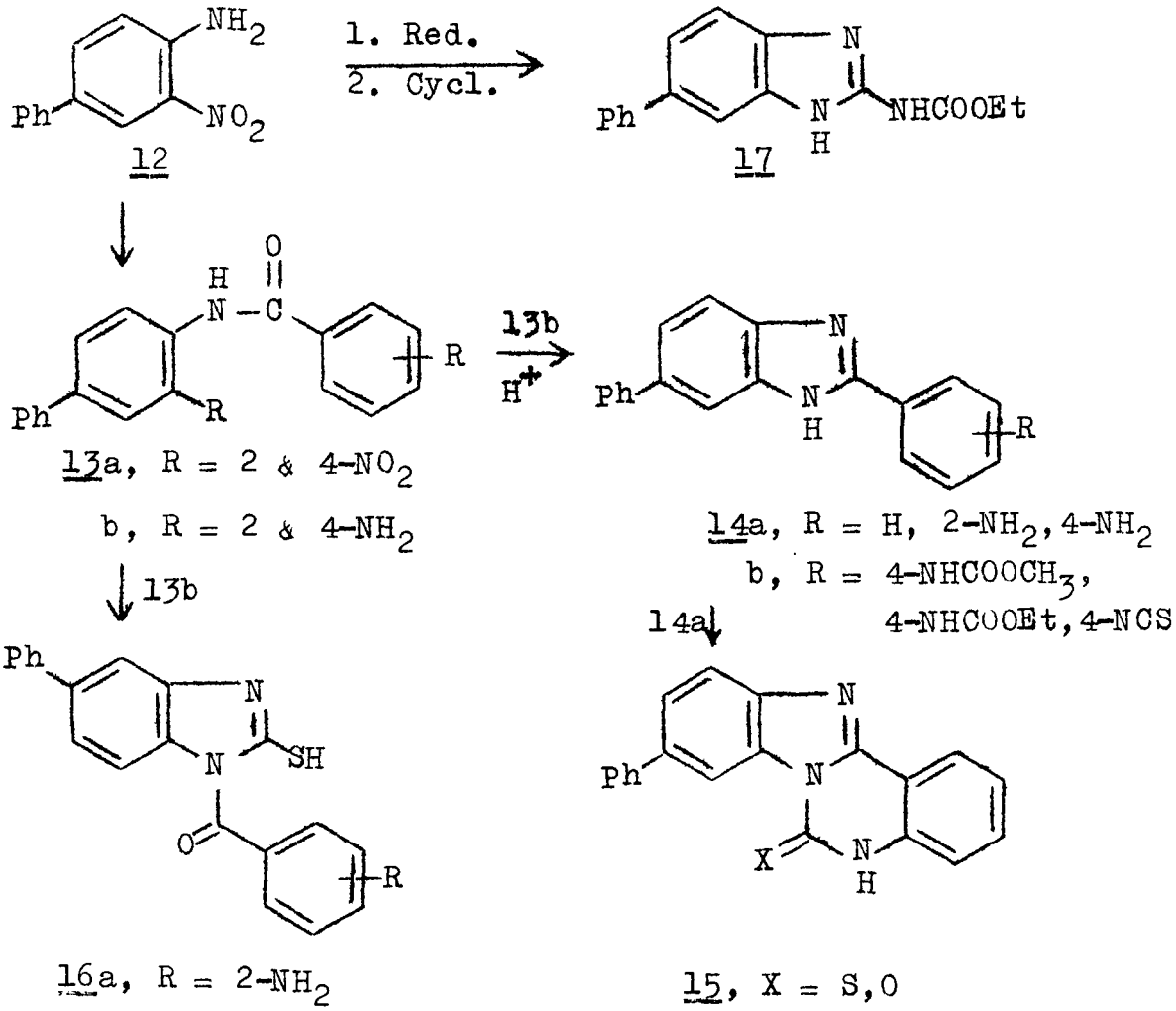
8a, R^1 = 3-NO_2, R = 4-NHAc
b, R^1 = 3-NO_2, R = 4-Cl



11, R = $NHCOOR^1$, H, CH_3
R^1 = CH_3, C_2H_5
X = S, SO_2, CO, CH_2, O
$S(CH_2)_2S$, CON⌒NCO

Synthesis of 2,5-diarylbenzimidazoles and their cyclic analogs

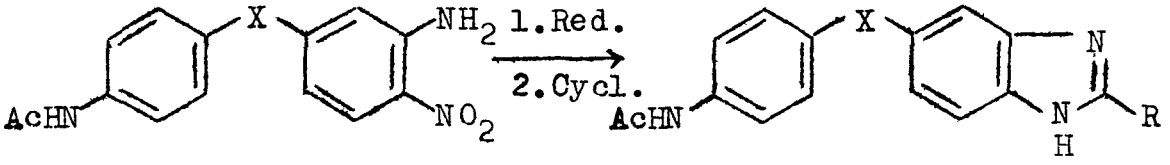
Synthesis of 2,5-diarylbenzimidazoles was undertaken based on the activity of several 2-arylbenzimidazoles. 4-Amino-3-nitrobiphenyl (12), on reaction with nitrobenzoyl chlorides, gave 4-(aroyl)amino-3-nitrobiphenyls (13a) which were reduced with hydrazine-hydrate and Raney-nickel to yield the corresponding amines 13b. Cyclization of 13b with acid gave 2,5-diarylbenzimidazoles (14a). Reaction of 2-(4-amino-phenyl)-5(6)-phenylbenzimidazole (14a, R= 4-NH_2) with alkyl chloroformates and thiophosgene yielded 2-(4-carbalkoxyaminophenyl and 4-isothiocyanatophenyl)-5(6)-phenylbenzimidazoles (14b). Similar reaction of 14a (R = 2-NH_2) with alkyl chloroformates and potassium ethyl xanthate yielded the cyclic products 15 while the reaction of 13b with thiophosgene yielded 1-(2-amino, 2-isothiocyanato and 4-isothiocyanatobenzoyl)-2-mercapto-5-phenylbenzimidazoles (16a-c). 4-Amino-3-nitrobiphenyl (12) was also used to prepare ethyl 5(6)-phenylbenzimidazole-2-carbamate (17) by reduction followed by cyclisation of the resulting amine with 1,3-dicarbethoxy-S-methylisothiourea[10].



2-Substituted-5(6)-(4-substituted phenoxy, phenylthio and sulfono)benzimidazoles

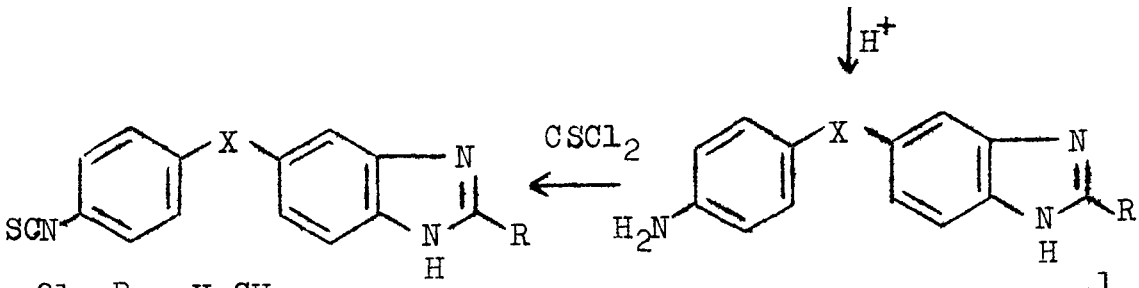
5-(4-Acetamidophenoxy and phenylthio)-2-nitroanilines (18) were used to prepare several benzimidazoles of the type 21. Reduction of 18 with hydrazine-hydrate and Raney-nickel and subsequent cyclization with formic acid, acetic acid and 1,3-dicarbalkoxy-S-methylisothioureas gave

the corresponding 2,5(6)-disubstituted benzimidazoles (19). Oxidation of 19 (X=S) with $KMnO_4$-CH_3COOH gave the sulfones 19 (X=SO_2). Acid hydrolysis of 19 with 10% HCl gave the corresponding amines (20) which were treated with thiophosgene to give 2-substituted-5(6)-(4-isothiocyanato-phenoxy, phenylthio and sulfono)benzimidazoles (21).



18, X = O,S

19, R = H, CH_3, $NHCOOR^1$
R^1= CH_3, C_2H_5
X = O,S,SO_2



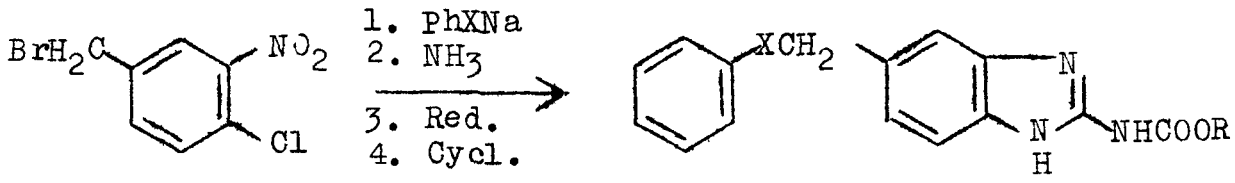
21, R = H, CH_3, $NHCOOR^1$
R^1= CH_3, C_2H_5
X = O,S,SO_2

20, R = H, CH_3, $NHCOOR^1$
R^1= CH_3, C_2H_5
X = O, S, SO_2

Synthesis of 5(6)-thiophenoxymethyl and phenoxymethyl benzimidazole-2-carbamates

The higher homologue (23) of fenbendazole was synthesized starting from 4-chloro-3-nitrobenzyl bromide (22) by the sequence of reactions described below. This has helped in evaluating the effect of introduction of one

methylene unit at 5(6)-position of benzimidazole on biological activity of fenbendazole.

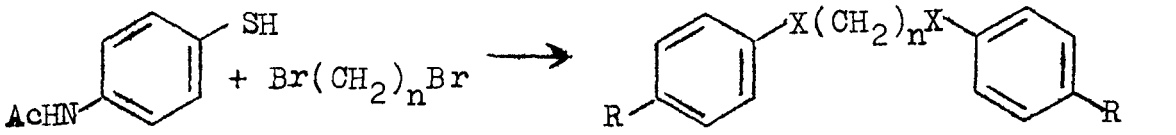


22

23, X = O, S, R = CH_3, C_2H_5

Synthesis of 1,2 and 1,3-disubstituted alkanes and 1,4-disubstituted piperazines

In order to study the change in biological activity of 4,4'-diisothiocyanatodiphenyl sulfide and sulfone by increasing the distance between two aryl functions by introduction of 2 or 3 CH_2 units, synthesis of 1,3- and 1,2-disubstituted alkanes (27) was undertaken. 4-Acetamidothiophenol (24), on reaction with 1,2-dibromoethane and 1,3-dibromopropane, yielded 1,2 and 1,3-di-(4-acetamidophenylthio)alkanes (25). Oxidation of 25 with $KMnO_4$-CH_3COOH gave the corresponding sulfones 25 ($X=SO_2$) which were hydrolysed in presence of acid to give the desired amines 26. Reaction of 26 with thiophosgene yielded the title compounds 27.



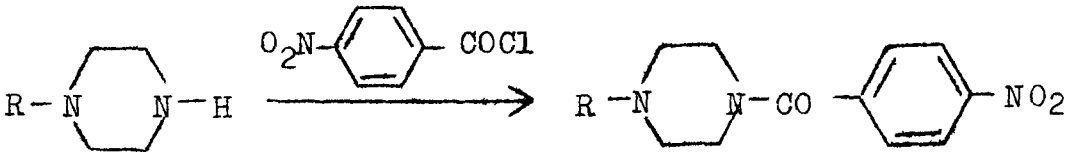
24

25, R=NHAc, X=S, SO_2, n=2,3

26, R=NH_2, X=S, SO_2, n=2,3

27, R=NCS, X=S, SO_2, n=2,3

The synthesis of compounds of the type 30 obtained by replacement of thio and sulfono linkage of 4,4'-diisothiocyanatodiphenyl sulfide and sulfone by piperazine moiety, a more active pharmacophore for antinematode activity, was also carried out. The synthesis starts with the reaction of either anhydrous piperazine or 4-nitrophenylpiperazine (28) with 4-nitrobenzoyl chloride to give 1,4-disubstituted piperazines (29). Reduction of 29 gave the corresponding diamines which were converted to isothiocyanates (30) by treating with thiophosgene.

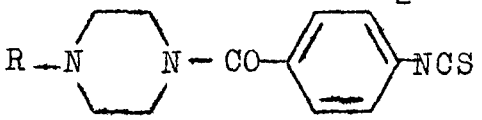


28, R=H, 4-nitrophenyl

29, R=4-nitrophenyl

R=4-nitrobenzoyl

↓ 1. Red.
↓ 2. $CSCl_2$



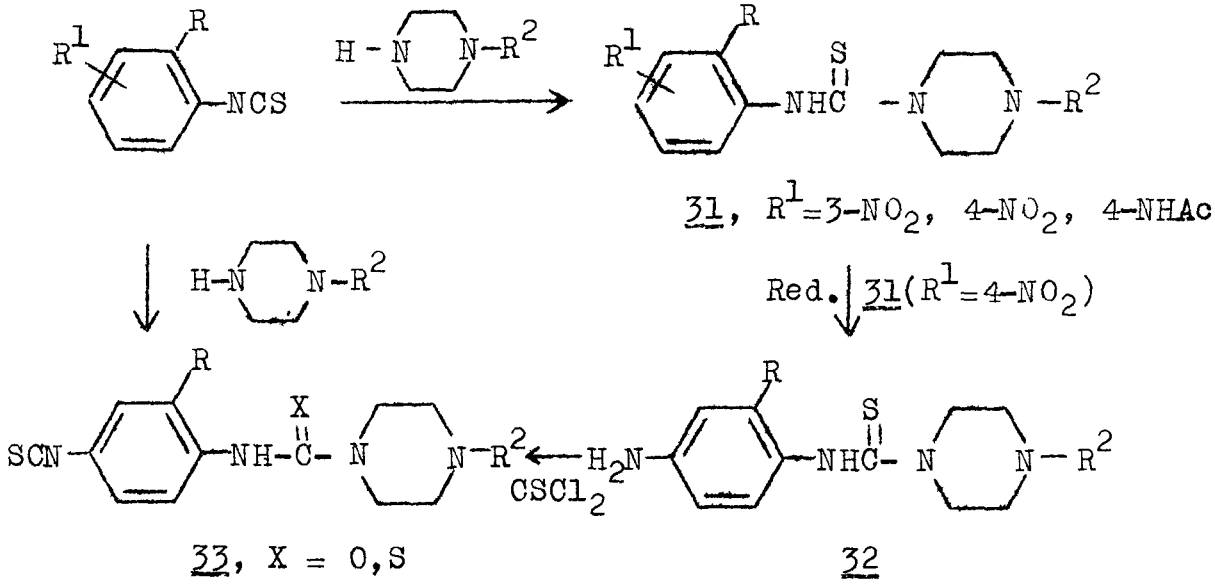
30, R=4-isothiocyanatophenyl

R=4-isothiocyanatobenzoyl

Synthesis of substituted thiocarboxamides, carboxamides and thioureas

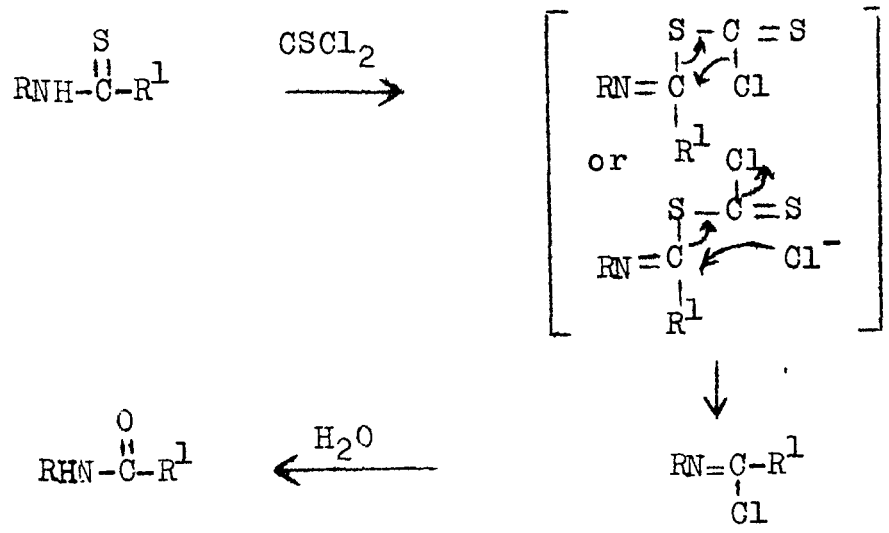
Several substituted thiocarboxamides, and carboxamides have been prepared as structural analog of bitoscanate. Reaction of different piperazines and anilines with

various phenylisothiocyanates gave the thiocarboxamides (31) which were reduced to the corresponding amines (32). Conversion of 32 into isothiocyanates by reacting with thiophosgene resulted in an unusual desulphurization of thiocarboxamides to give carboxamides (33, X=O). Thiocarboxamides (33, X=S) carrying the isothiocyanato function were conveniently prepared by reaction of one mole of piperazines with p-phenylenediisothiocyanate (bitoscanate). Several thioureas were also prepared either by reaction of 2-aminobenzimidazole or 4-aminoacetanilide on substituted phenylisothiocyanates[11].



The unusual desulphurization of thiocarboxamides and thioureas with thiophosgene was studied by converting a number of thiocarboxamides, thioureas and thiamide to their corresponding oxygen analogs with the help of

thiophosgene and possible mechanism for desulphurization has been proposed[12].



Biological Activity:

Most of the compounds have been evaluated for their anthelmintic activity against Nippostrongylus brasiliensis in rats, Nematospiroides dubius in mice, Ancylostoma ceylanicum in hamsters and Hymenolepis nana in rats and mice. A large number of 2,5-disubstituted benzimidazole derivatives showed promising antihookworm and anticestode activity which is reported in the thesis. The best compounds of this study were found to be 2,2'-dicarbomethoxyamino-5,5'-dibenzimidazolyl oxide (11, X=O, R=$NHCOOCH_3$) and sulphide (11, X=S, R=$NHCOOCH_3$) which exhibited 100% removal of A.ceylanicum at a single oral dose of 12.5-25 mg/kg in hamster while 100% of the H.nana worms were expelled by 2,2'-dicarbomethoxyamino-5,5'-dibenzimidazolyl sulfide (11, X=S, R=$NHCOOCH_3$) and

methyl 5(6)-(4-isothiocyanatophenylthio)benzimidazole-2-carbamate (21, X=S, R=$NHCOOCH_3$) at single oral doses of 70 and 30 mg/kg respectively from rats. Compound 11 (X=O, R=$NHCOOCH_3$) was 100% effective in causing complete eradication of H.nana from rats at a single oral dose of 250 mg/kg. The results of the in vitro antimicrobial activity of some of the compounds are also reported in the thesis.

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JUNE, 1982

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June 8,1982

CERTIFICATE

This is to certify that the work embodied in this thesis has been carried out by Mr.Syed Abuzar under our supervision. He has fulfilled the requirements for the degree of Doctor of Philosophy of the Aligarh Muslim University regarding the nature and period of investigational work. The work included in this thesis has not been submitted for any other degree and, unless otherwise stated, is all original.

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Reader
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S.Abuzar

June 1982.
Med.Chem.Div.

(Syed Abuzar)

C O N T E N T S

LIST OF ABBREVIATIONS

Ac	: acetyl
Ar	: aryl
Arom	: aromatic
Bu^{n}	: n-butyl
Calcd.	: calculated
cm	: centimeter
Compd.	: compound
DMF	: dimethyl formamide
DMSO	: dimethyl sulfoxide
d	: doublet
Et	: ethyl
g	: gram
hr	: hour
IR	: infra red
Lit.	: literature
M^{+}	: molecular ion peak
m	: meta
m.p.	: melting point
m	: multiplet
Me	: methyl
NMR	: nuclear magnetic resonance
o	: ortho
p	: para

Ph	: phenyl
Pr	: propyl
Pr^i	: iso-propyl
q	: quartet
s	: singlet
t	: triplet
TFA	: trifluoroacetic acid
THF	: tetrahydrofuran
TLC	: thin layer chromatography
TMS	: tetramethyl silane

PREFACE

The success in successful eradication of helminthiasis depends on the proper use of a broad-spectrum anthelmintic drug and strict prophylactic regulations followed by the patients. Both these requirements have been met to a great extent in several advanced countries of the world leading to complete elimination of the several forms of helminthiasis from the population. However such a situation does not prevail in different parts of the third world and even some advanced nations.

The habit and habitat, poor sanitation, low living standards and occupational needs are the main criterions for the profound increase in helminth infestations all over the world which has been partially manifested due to lack of a suitable drug. This has also helped in giving rise to multiple infection which, many a times poses serious clinical complications and is difficult to cure. Recent surveys have indicated the high prevalence of intestinal helminthiasis of which infestations due to hookworms and cestodes are particularly important.

In the agriculture-based countries like India, the hookworm infections have a great bearing with the health, general well-being and socio-economic development of the rural masses because of the blood-sucking nature of

the parasites. Cestodes are equally important intestinal helminths because of the potential danger of producing cysticercosis by them. Thus there is a great deal of concern over evolving an anthelmintic which would not only eliminate the roundworms but also simultaneously remove tapeworms, if present, from the gastrointestinal tract of the man. The present work is mainly directed towards the synthesis of potential anthelmintic agents showing activity against hookworms and cestodes.

The first chapter of the thesis deals with the present status of the disease caused by hookworms and cestodes and the various classes of compounds discovered to treat these infections in man and animals. The second chapter covers the synthesis of various substituted-5(6)-N-heteroarylbenzimidazolesand benzthiazoles. In addition a series of 2,2'-disubstituted-5,5'-dibenzimidazoles and 2,5-disubstituted benzimidazoles have been synthesized as the structural congeners of benzimidazole anthelmintics. A number of 1,2- and 1,3-disubstituted alkanes and 1,4-disubstituted piperazines have also been prepared. A series of thiocarboxamides, carboxamides and thioureas have been synthesized and the mechanism of thiophosgene induced desulphurisation of these compounds is studied.

The compounds, thus synthesized, have been evaluated

for their antihookworm activity against *Nippostrongylus brasiliensis* in rats, *Nematospiroides dubius* in mice and *Ancylostoma ceylanicum* in hamsters, anticestode activity against *Hymenolepis nana* in mice and rats and *in vitro* antimicrobial activity against different strains of bacteria and fungi; all these screening results are reported in the present thesis.

Chapter I

RECENT DEVELOPMENTS IN THE TREATMENT OF HOOKWORMS AND CESTODE INFECTIONS

The gastrointestinal tract of man is the most common seat of predilection for several infective diseases apparently because of the abundance of ideal conditions for survival and replication of the parasites. The intestinal helminth infections constitute one of the most widely prevalent disease of man affecting nearly 2500 million people around the world[1]. A number of helminths parasitizing the gastrointestinal tract are asymptomatic and rarely cause much trouble to the host while a few bear great public health significance and also hamper the socio-economic development by inhibiting the production of milk, meat, wool and leather in several third world and developing countries of the world. The hookworms and the cestodes are two important helminth parasites which have recently attracted the closer attention of medicinal chemists, parasitologists and clinicians because of their world-wide prevalence, greater pathogenic significance and concomitant detrimental effects on human body functions.

Among the measures available today for treating intestinal helminthiasis, the chemotherapeutic approach seems to be quite rational and deserve detailed work out. During the last two decades several newer classes of compounds

have been synthesized which have provided definite advantage over the classical antihookworm and anticestode drugs. The present review is mainly concerned in providing a precise account of the recent developments in the chemotherapy of hookworm and cestode infections in man and domestic animals. A detailed account of the classical anthelmintics used to treat various forms of intestinal helminthiasis is available[2-8].

1. The Hookworm Infections

The hookworm infections, chiefly prevalent in the rural population of agriculture based regions of the under developed world, is acquired by walking bare foot in damp soil contaminated with infective larvae. The hookworm larvae penetrate the skin and migrate to lungs and finally to intestine where they develop into adult worms and live on the direct blood feed of the host. The disease is distributed widely in the tropical and sub-tropical regions of the world; however it is endemic in India, China, Japan, Central America, Mexico, Panama, West Indies, Venezuela, Peru, Argentina, Paraguay and various parts of Northern and Eastern Africa. It is estimated[1,9] that more than 700-800 million people around the world are the victims of hookworm disease. In India the infection is common in farmers working in rice, banana, maize and potato fields and affects nearly 205 million[10] people in Assam, Bengal,

Bihar, Orissa, Kerala, Madras, Uttar Pradesh and other parts of the country.

The hookworms are endoparasitic nematodes found attached to the mucosa of the intestinal wall. The common hookworms which infect man are Ancylostoma duodenale, Ancylostoma ceylanicum and Necator americanus. The domestic animals are also infected by various hookworms like Ancylostoma caninum (dogs), Ancylostoma braziliense (cats), Bunostomum trigonocephalum (cattle) and Giaigeria pachyscelis (sheep and goats).

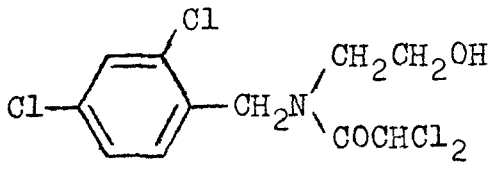
The main clinical manifestations of this disease are marked hypochromic microcytic anaemia leading to general weakness, fatigue and lack of physical and mental growth and reduced productivity of the host. In addition, the patient may also experience abdominal pain, constipation, anorexia and giddiness.

1.1 Chemotherapy of hookworms

1.11 Older drugs

The classical drugs which have been used to treat various human and animal hookworm infestations were drawn chiefly from halogenated hydrocarbons (tetrachloroethylene[11] and mantomide (1)[12] etc.) and substituted phenols (2,4,5-trichlorophenol (2)[13], 4-cyano-2-iodo-6-nitrophenol (3)[14] etc.); however their clinical use was limited due to their

low activity and narrow margin of safety and, therefore, have been replaced slowly by more active drugs. Another group of compounds showing a wide range of pharmacological and antiparasitic activity are the quarternary ammonium salts of which bephenium hydroxynaphthoate (4) was developed by Wellcome laboratories as human antihookworm drug[15]. Bephenium hydroxynaphthoate has been recommended at a dose of 5 g (=2.5 g of base) per adult showing 28-90% clearance of N.americanus[16-18] and 80-100% clearance of A.duodenale



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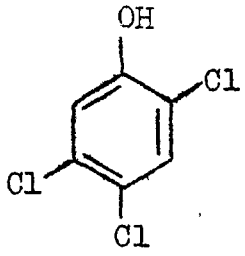

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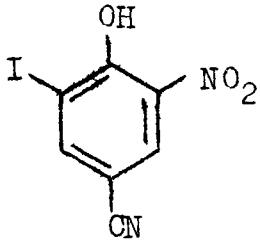

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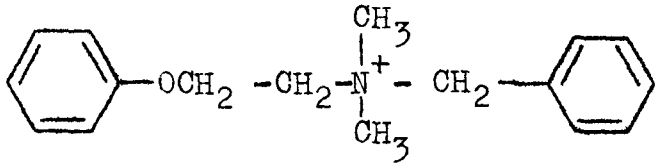

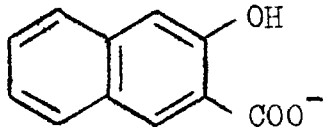

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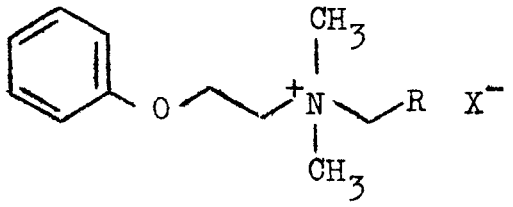
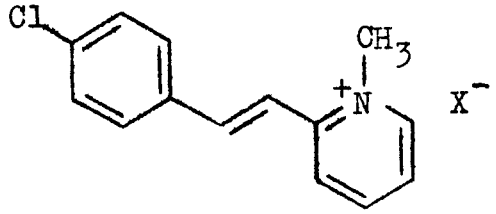
infection[19,20]. However, the drug is toxic,bitter in taste and produces several side effects. Following the discovery of bephenium, a large number of its structural analogs were synthesized but none surpassed the potency of the parent drug[21-28]. The most active congeners of bephenium were

thenium (5)[26], diphezyl (6)[27] and styrylpyridinium (7)[28] but none proved its usefulness in treating clinical hookworm infections and were confined in controlling canine and feline hookworm diseases.





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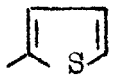
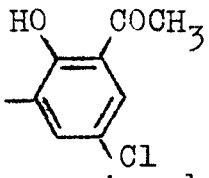
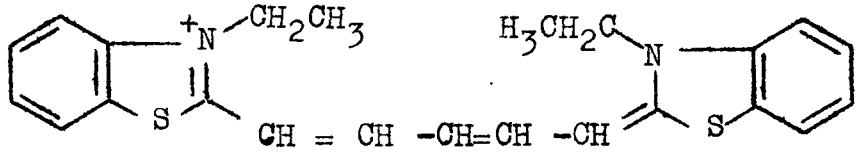
5, R = 

6, R = 

A few cyanine dyes have also been used in the treatment of hookworm infestations in man and animals; the most important being dithiazanine (8) which is given to patients having N.americanus and A.duodenale infections with variable activity[29,30].



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1.12 New candidate antihookworm agents

Benzimidazoles

The first truely modern anthelmintic was thiabendazole (9) discovered in 1961 by Merck[31]. The drug shows high

Table 1 Details of some potent benzimidazole anthelmintics

No.of Drug	Name of Drug (Discover)	Year	Activity in animals	Activity in humans	Dose in mg/kg
1	2	3	4	5	6
9	Thiabendazole (Merck)	1961	Active against A.caninum in dogs and other hookworms in sheep and cattle.	Active against A.duodenale and N.americanus and cures creeping eruption caused by A.braziliense.	25-100 for 1-6 days.
10	Cambendazole (Merck)	1970	Active against A.caninum in dogs and other hookworms in pets.	-	100
11	Parbendazole (Smith Kline & French)	1967	Eliminates A.caninum from dogs.	-	20
12	Mebendazole (Janssen)	1971	Active against N.brasiliensis, A.ceylanicum and A.caninum in mice hamsters and dogs.	Removes A.duodenale and N.americanus from man.	100*
13	Oxibendazole (Janssen)	1973	Active against various nematodes in mice,sheep,cattle	- & horses.	50

1	2	3	4	5	6
14	Fenbendazole (Hoechst)	1974	Active against *A. caninum*, *U. stenocephala* and *H. contortus* in dogs, sheep and goats.	Active against *N. americanus*.	25-50
15	Oxfendazole (Syntex)	1975	Active against various nematodes in calves, lambs and goats.	-	5
16	Albendazole (Janssen)	1975	Effective against *A. caninum* and *B. phlebotomum* in dogs and cattle.	-	50
17	Flubendazole (Janssen)	1978	Highly effective against nematodes and cestodes in rodents, chicks, pigs, dogs and sheep.	Eliminates *N. americanus* and other nematodes from man.	10-100
18	Ciclobendazole (Janssen)	1977	Active against nematodes in rodents.	Eliminates hookworms and other nematodes; as active as mebendazole.	600 (optimal)

*Given at a dose of 100 mg/adult for 3 days.

activity against human hookworms at a dose of 25-100 mg/kg given in a single or multiple doses[32-34]. Thiabendazole is one of the most active drugs for treating creeping eruption caused by the larvae of A.braziliense in man. At a dose of 50 mg/kg given orally[35,36] or applied locally[37,38], it effectively cures the lesions.

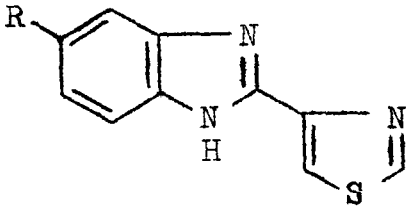
The discovery of thiabendazole stimulated a world-wide research resulting in the evolution of a series of powerful anthelmintics 10-18 (Table 1). The most potent members of this series are mebendazole (12) and fenbendazole (14). Mebendazole possesses high activity against a number of species of nematode and cestode parasites in different hosts. The drug causes complete clearance of Nippostrongylus brasiliensis in mice[39], A.ceylanicum in hamsters[40] and A.caninum in dogs[41] and has been recommended as an ideal anthelmintic for small animals[42]. Mebendazole is equally effective in eliminating N.americanus and A.duodenale infections in adult and child patients at a dose of 100 mg/ adult given twice a day for 3 days[43-45]. The children accordingly receive lower dosages.

Fenbendazole (14) exhibits potent activity against different species of lung worms and intestinal nematodes. It gives high cure rates against A.caninum in dogs[46] and Haemonchus contortus in sheep and goats[47,48] at a dose of

50 and 5 mg/kg respectively. When given at a dose of 100 mg/kg it also eliminated N.americanus in man[49].

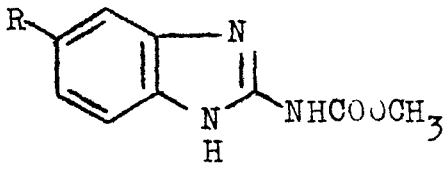
The other 'bendazole' anthelmintics have also been used successfully to treat hookworms infections in cattle, sheep, goats, poultry and pets with good success[50]. Some of them, like flubendazole (17)[51] and ciclobendazole (18)[52] have shown promising results in treating human hookworm diseases.

The majority of benzimidazole anthelmintics were earlier shown to exert their activity by inhibiting the fumarate-reductase enzyme activity of the parasites which plays crucial role in worms anaerobic cycle. The inhibition of this step in the metabolism would cut-off the energy supply of the worm leading to its paralysis. Later the activity of various benzimidazole anthelmintics (9-18) has been attributed to their ability to bind with mammalian tubulin and to inhibit the assembly of microtubules[53]. Mebendazole is known to disrupt cytoplasmic microtubules resulting in degeneration of Ascaris suum intestinal cells[54]. More recently it has been shown that mebendazole and fenbendazole bind (inhibition constants 1.9×10^{-8} and 6.5×10^{-8} respectively) with embroyonic tubulin of A.suum which has been carried out by inhibition studies with ^{3}H



9 , R = H, Thiabendazole

10, R = NHCOOPr^{i}, Cambendazole



11, R = Bu^{n}, Parbendazole

12, R = COPh, Mebendazole

13, R = OPr, Oxibendazole

14, R = SPh, Fenbendazole

15, R = SOPh, Oxfendazole

16, R = SPr, Albendazole

17, R = $COC_6H_4F(p)$, Flubendazole

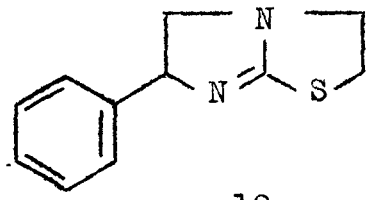
18, R = CO-◁ , Ciclobendazole

colchicin[55,56]. Thus the anthelmintic action of benzimidazole anthelmintics may be due to their differential binding affinities between nematode and mammalian tubulin (the inhibition constant of mebendazole and fenbendazole for bovine brain tubulin is 250-400 times higher than for A. suum embryonic tubulin).

Imidazolines

In a follow up study of the potentiality of imidazolines in parasite chemotherapy, Janssen Pharmaceutica came out with a new broad spectrum anthelmintic, tetramisole (19)[57]. Tetramisole is a racemic mixture of R- and S-, 2,3,5,6-tetrahydro-6-phenylimidazo [2,1-b]thiazole which have been resolved and their absolute conformation established[58]. The anthelmintic activity of tetramisole is due to its

S(-)-isomer called levamisole[58]. Levamisole possesses high activity against different gastrointestinal nematodes of sheep, dogs, swine, fowl, cattle, horses and man. At a dose of 2.5 mg/kg given orally it eliminates various round worms including hookworms in man and shows fewer side effects[59,60]. Levamisole is a potent inhibitor of fumarate-reductase in various nematodes[61] and shows immunostimulant properties in man and animals[62]. The R(+)-isomer, surprisingly has antidepressant activity.



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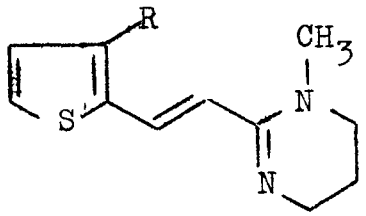
Pyrimidines

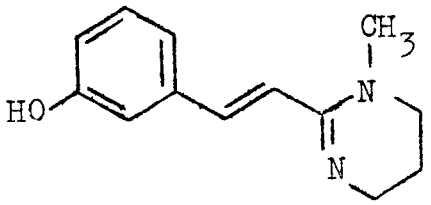
Tetrahydropyrimidines are another class of compounds with potent anthelmintic activity which has been studied extensively at Pfizer laboratories. The most active member of this series is pyrantel (20)[63]. Pyrantel pamoate has been found to give 75-91% cure rates against *N. americanus* and *A. duodenale* in man[64] at a dose of 10-100 mg/kg depending upon the nature and intensity of the infections. It is equally effective against various intestinal helminths of sheep, goats, dogs, cattle, horse, swine and fowl.

The structural modifications of pyrantel have led to the synthesis of a large number of its molecular congeners of which morantel (21)[65] and oxantel (22)[66-68] have shown high promise in curing different nematode infections in man and animals.



20, R = H, Pyrantel

21, R = CH_3, Morantel

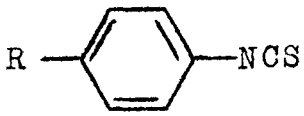


22, Oxantel

Isothiocyanates

Among the several aryl isothiocyanates possessing high nematodicidal activity, phenyl isothiocyanate (23) and 1,4-phenylenediisothiocyanate (24, bitoscanate, developed by Hoechst) show high antihookworm activity in man. 23 has been demonstrated to cure human hookworm infections at a dose of 300 mg/kg given in three divided doses[69]. Clinical studies carried out with bitoscanate have shown that the drug gives 47-96% and 25-96% cure rates against A.duodenale and N.americanus infections respectively at a dose of 3 x 100 mg for adults and 2 x 100 mg for children given at 12 hr intervals[70-72]. The side effects of bitoscanate are nausea, vomiting, headache, abdominal pain and weakness which

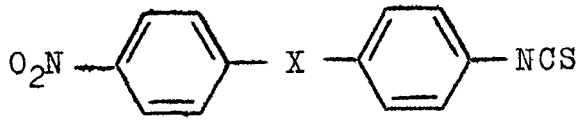
are generally mild and transient.



23, R = H

24, R = NCS, Bitoscanate

Recently Ciba laboratories have introduced 4-isothiocyanato-4'-nitrodiphenylamine (25, amoscanate) for treatment of hookworm and other nematode infections in man[73]. Three doses of this compound at 100, 125 or 250 mg at 8 or 12 hr intervals were found to cause complete removal of A.duodenale and N.americanus in man[74-76]. The oxygen analogs of amoscanate is nitroscanate (26) which eliminates hookworms from cats and dogs[77].



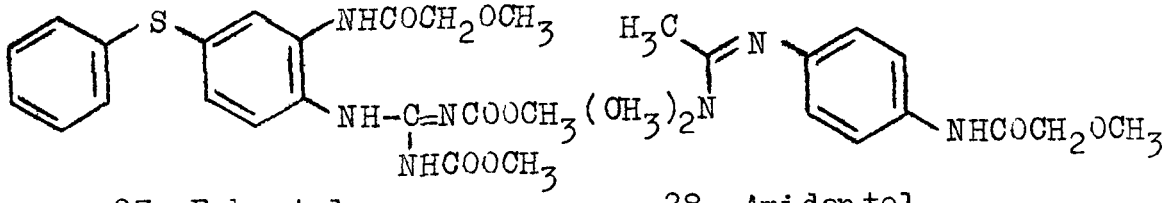
25, X = NH, Amoscanate

26, X = O, Nitroscanate

1.13 Recent antihookworm agents

Febantel (27) and amidantel (28) are the two new anthelmintic developed by Bayer. Febantel shows high activity against different species of nematodes and cestodes in mice, rats, dogs, sheep and cattle. At a dose of 1-5 mg/kg it eliminated A.caninum, Uncinaria stenocephala, Nematospiroides

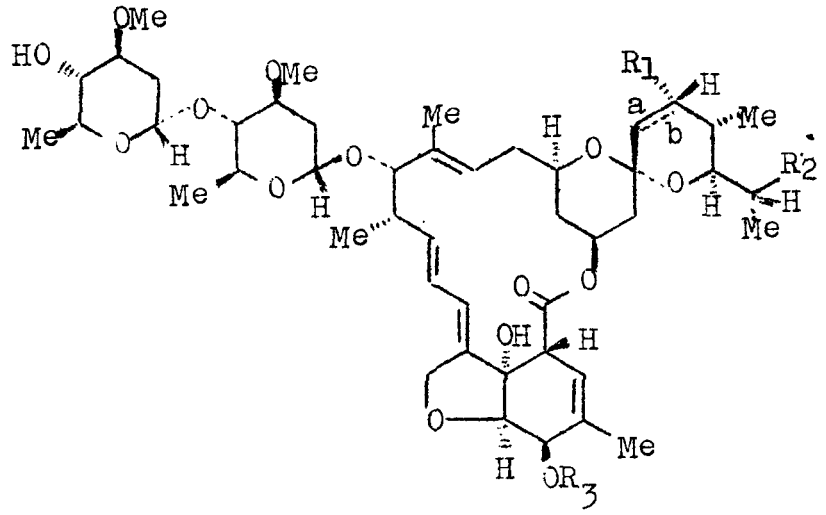
dubius, H.contortus and B.trigonocephalum from various animals[78,79]. Amidantel also clears Nippostrongylus muris, N.dubius and A.caninum at a dose of 250 x 3, 250 x 4 and 25 mg/kg respectively[80,81].



27, Febantel

28, Amidantel

A series of avermectins (29), produced by Streptomyces avermitilis, have been developed at Merck laboratories which show high order of antiparasitic activity[82]. Avermectin B_{1a} and B_{2a} possess marked activity against A.caninum and A.braziliense in dogs at an oral dose of 0.003-0.005 mg/kg[83]. Later it was demonstrated that compounds of this class are highly effective against various gastrointestinal helminths of sheep and cattle at an oral dose of 0.05-3 mg/kg[84].



29, Avermectin

2. The Cestode Infections

The cestode infections are generally considered as the helminth diseases of minor importance as compared to nematode and trematode infections. This is probably because the cestodes produce lesser pathogenic manifestations and are prevalent in smaller section of the population. The comparative rate of incidence of various helminth diseases would indicate that nearly 2500 million people are infected with intestinal nematodes[1] while 200 million subjects harbour schistosomiasis[6,85]. In contrary, about 100 million people are the victims of intestinal cestodes all over the world[1,86,87].

Although the incidence of cestode infections is not as high as other helminth infestations, they have a distinct influence on the human and animal health, and are generally difficult to eradicate. In addition, the risk of acquiring cysticercosis and hydatid disease poses potential danger of producing several serious and grave clinical manifestations for which an ideal remedy is yet to be discovered.

The cestodes, infecting man, possess a world-wide distribution; however, they are chiefly prevalent in the tropical and subtropical regions. The endemic areas of this infection are Iran, Iraq, Israel, Jordan, Lebanon,

Saudi Arabia, Syria, Turkey, Pakistan, India, Tibet, Korea, Japan, U.S.S.R., different parts of Africa, Mexico, Brazil, Peru and Chile. The cestode infections have also been reported from some parts of Europe, Australia and America.

Like hookworms, the cestodes are also endoparasitic, hermaphrodite tape like helminths living in the alimentary canal of the vertebrates. The main cestodes infecting man are Taenia saginata (beef tapeworm), T.solium (pork tapeworm), Diphyllobothrium latum (fish tapeworm) and Hymenolepis nana (dwarf tapeworm). The important cestodes infecting animals are Dipylidium caninum and D.mansoni (cats and dogs), Moniezia expansa (sheep), T.pisiformis (dogs, foxes), T.hydatigena (dogs), T.taeniformis (cats) and Raillietina cesticillus (fowls).

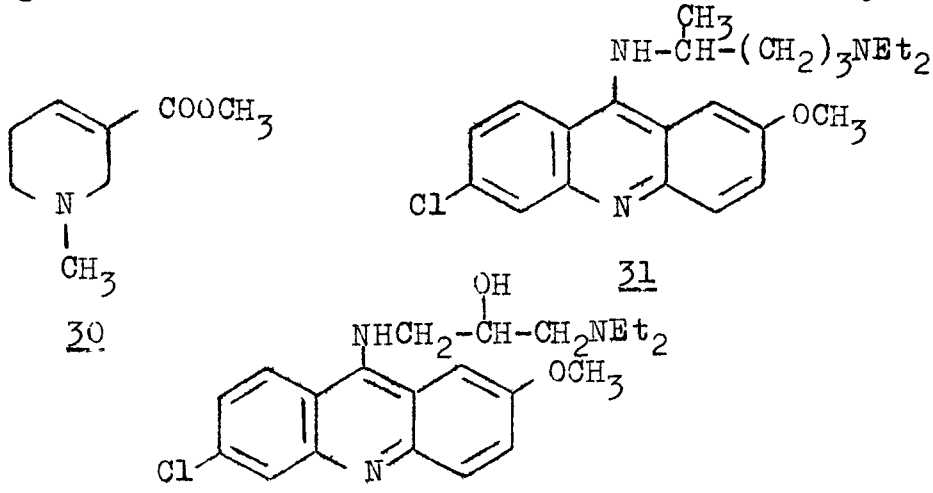
The life cycle of cestodes normally requires one intermediate host such as cattle, pigs and fishes. Man acquires this infection by eating poorly cooked infected beef, pork or fish; the cysticerci present in the flesh emerge out and attach themselves to intestinal wall where they grow, attain maturity and live for several years with the host. The cestode infections are generally asymptomatic; however the patient may suffer from nausea, diarrhea, hunger pains, weakness, malaise, weight loss and anaemia.

The cysticerci may migrate in any part of the body and cause several complications. The cysts may cause blindness and nervous disorders if migrate in eye and brain respectively.

2.1 Chemotherapy of Cestodes

2.11 Older drugs

A number of plant products such as Aspidium oleoresin (extract of male fern, Dryopteris mas)[4], arecoline (30)[88], pumpkin seeds[89-91] have been used since long for treating human cestodiasis. Several tin compounds have been shown to possess high activity against different cestode parasites in man and animals[92]. A few derivatives of acridines such as quinacrine (31)[93-95] and acranil (32)[96,97] were used earlier to cure cestode infections in man. In general these drugs showed several toxic effects in hosts, required intensive medical care of the patients and also did not cause complete elimination of the infection. Due to these shortcomings better chemotherapeutic agents were discovered which slowly replaced older drugs in the clinical treatment of cestodiasis.



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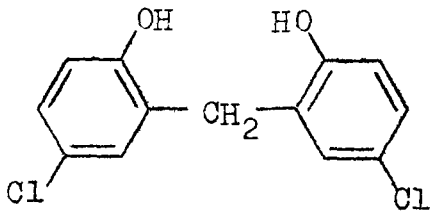
2.12 New Anticestode Drugs

Dichlorophene (33)

This is an old antimicrobial, germicidal and fungicidal agent which has been found to eliminate T.pisiformis and D.caninum from dogs and cats at a dose of 200 mg/kg[98-100] and Moniezia sp. from sheep at a dose of 150 mg/kg[101,102].

The drug has been extensively used since 1959 to treat T.saginata infection in man[103-105]. The usual recommended adult dose of dichlorophene is 60-100 mg/kg not exceeding 5 g in a day; the children receive accordingly smaller doses. The cure rates were between 50-86%. Dichlorophene is usually safe at therapeutic doses and does not produce any side effects; however some allergic reactions may be noticed[106]. At higher doses the drug may produce nausea, vomiting, diarrhea, colic and jaundice and may require special care to patients with heart and liver diseases.

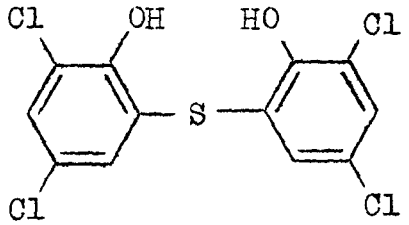


33, Dichlorophene

Bithionol (34)

This was initially used as an antimicrobial and topical antiseptic agent but later found to exhibit activity against a wide range of cestode parasites in men and animals. It caused 70-85% removal of T.hydatigena, T.ovis and M.multiceps at a dose of 150 mg/kg while all the D.caninum worms from dogs were eliminated at a dose of 150-200 mg/kg and no side effects were observed except occassional diarrhea and softening of faeces[107]. The drug showed 100% efficacy against Moniezia and Anoplocephala species in sheep at a dose of 100 mg/kg[108,109].

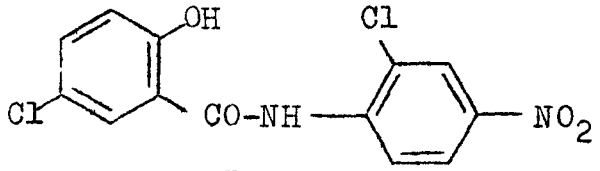
Bithionol has also been used successfully to treat T.saginata and D.latum infections in man[110-113]. A dose of 40-60 mg/kg, given once or in two divided doses, was sufficient to cure patients infected with T.saginata or D.latum; however scolex was removed only in 37.5-50% of the cases. The common side effects of this drug are nausea, vomiting, anorexia, general fatigue and epigastric pain[112]. High cure rates in human cestodiasis have also been obtained when the patients were given a combination of 0.5-1 g of bithionol with 1-2 g of niclosamide[114,115].



34, Bithionol

Halogenated salicylanilides

Niclosamide (Yomesan, 35) is the first member of this class which was introduced in 1960 by Bayer[116,117] and since then it became the primary drug to treat different forms of tapeworm infections in man and animals. In the preliminary experiments carried out on animals, it showed high cure rates against T.hydatigena, M.multiceps and D.caninum in dogs at a dose of 50 or 100-300 mg/kg[118,119]. At lower dosages (110-200 mg/kg) also, given in capsules or in food, it eliminated all T.pisiformis and D.caninum infections from dogs[120]. Later it was demonstrated that niclosamide can cause complete eradication of T.hydatigena in dogs at a dose as low as 32 or 62 mg/kg[121]. The drug is also highly effective against D.caninum (250 mg/kg)[119] and H.taeniaeformis (750 mg dose or 100-200 mg/kg) in cats[122,123].



35

Sheep infected with M.expansa and M.benedeni were completely freed of tapeworms when treated with niclosamide at a dose of 75 mg/kg and no toxic effect was observed[124-126]. It was also highly effective against Raillietina in chickens at a dose of 20-25 mg/kg[127,128].

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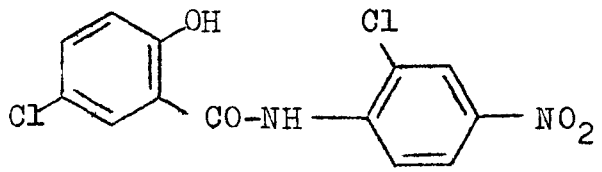

35

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In clinical practice niclosamide has shown excellent results in treating practically all human tapeworm infections[129-137]. Patients suffering with D.latum and H.nana infections were given 2-4 chewable tablets (each containing 1 g of niclosamide) after breakfast when all the cases were cured with minor side effects[138]. It cured Diphyllobothrium infection in several patients when given 1 g/adult followed by 1 g/adult after two hours and then a saline purge after 3-4 hours[139].

Treatment of H.nana infection in adult and child patients can be carried out at different dose schedules. When niclosamide was given at a dose of 1 g per adult daily for 6-13 days, the drug gave 74-75% cure rates against H.nana[140,141]. Better results were obtained against the above infection by giving the patients 60 mg/kg of the drug followed by 15 mg/kg for 6-7 days[142,143]. Children infected with H.nana were given 0.5 g of niclosamide daily for 6 days or a single dose of 100-130 mg/kg of the drug when high cure rates were achieved[140-144].

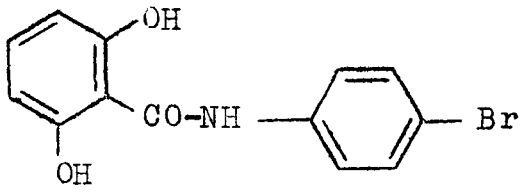
Niclosamide has also been found to possess high activity against T.solium and T.saginata in man. A dose of 2-3.5 g/adult given in single or divided doses with or without a saline purge, has been found to cure 85-97% of patients infected with T.solium and T.saginata[138,139,142,145-14

Niclosamide is practically devoid of any

contra-indication and may be used safely during pregnancy also[150]. The drug possesses low toxicity which is probably due to its poor absorption through the intestinal wall.

Based on the high activity exhibited by niclosamide, Hoechst laboratories introduced 4'-bromo-γ-resorcylanilide (Terenol, 36) as an useful veterinary cestodicidal agent[151,152]. At a dose of 10-25 mg/kg, terenol eliminated H.diminuta from rats[151]. It was equally effective against Moniezia in cattle and goats at a dose of 0.5 ml of suspension (65 mg of terenol)/kg body weight when 100% clearance of the tapeworms were observed[153-155].

Oxyclozanide (37) is a polyhalogenated analog of niclosamide developed by ICI laboratories[156]. The drug removed 13 day old H.diminuta from rats at a dose of 4 mg/kg. It is a well tolerated compound which destroyed the 7 day old H.diminuta in mice at the similar dose given in above experiment[157].



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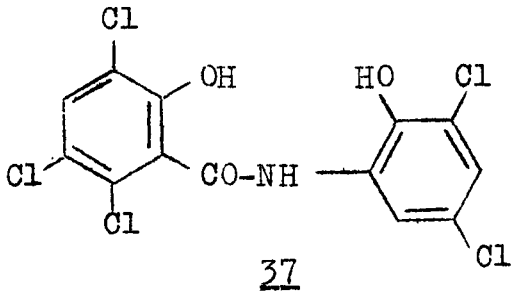
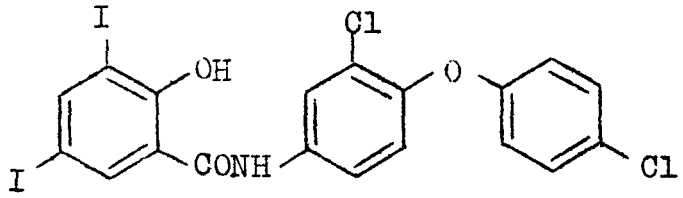


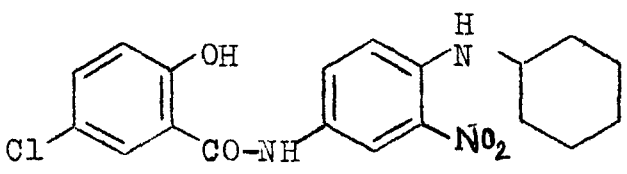
37

Merk Sharpe and Dhome developed a diiodo analog of niclosamide, rafoxamide (38) which showed cestodicidal activity in rodents infected with H.nana and H.diminuta[158].



38

During the search of more potent congeners of niclosamide, a large number of substituted salicylanilides have been prepared at this laboratory many of which exhibit cestodicidal activity superior to that of parent drug[7,159-168]. Thus, a series of 5-chloro-3'-nitro-4'-substituted salicylanilides were found to possess high anticestode activity[160-163]; the best compound of the series was 5-chloro-3'-nitro-4'-cyclohexylaminosalicylanilide (39) which eliminated all the worms of H.nana in mice at a dose of 30-50 mg/kg[160]. Similarly 2'-chloro-4,4'-dinitrosalicylanilide (40) and 4',5-dichloro-3'-nitrosalicylanilide (41) cleared 100% of H.nana infection in mice at a single oral dose of 250 mg/kg[162].



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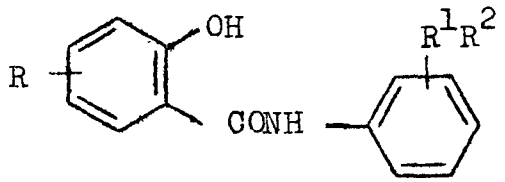
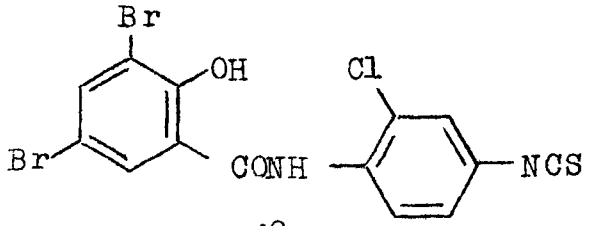


40, R = R^1 = 4-NO_2, R^2 = 2-Cl

41, R = 5-Cl, R^1 = 4-Cl, R^2 = 3-NO_2

A series of substituted-3,5-dibromosalicylanilides have been prepared many of which caused 100% eradication of H.nana from rats and mice at a dose of 10-250 mg/kg[164,165]. The best member of this series was 3,5-dibromo-2'-chloro-4'-isothiocyanatosalicylanilide (42) with marked anthelmintic activity and would be discussed later.

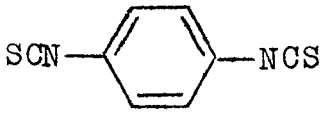


42

Isothiocyanates

Bitoscanate (43) is the first member of this class which was developed by Hoechst laboratories in 1960's to treat hookworm and cestode infections in man and animals[169]. At a dose of 6 mg/kg it showed high activity against T.pisiformis in dogs[170]. It also eliminated 99.2-100% of the H.nana worms from mice when given at a dose of 50-170 mg/kg[171,172].

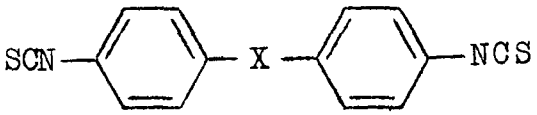
Clinical studies with bitoscanate showed that the drug was effective in eliminating H.nana from children (5-9 years old) at a dose of 200 mg/kg given in two divided doses at 12 hours interval. The cure rate was 67%. The older children and adult patients needed 300 mg/kg (in three doses of 100 mg, 12 hours apart) to yield 95% cures against H.nana infection[173].



43

A series of substituted diphenyl sulfides, disulfides, sulfoxides, sulfones, ethers, methanes, ketones and ethylenes carrying an isothiocyanato group in one or both the phenyl rings have been synthesized of which 4,4'-diisothiocyanatodiphenyl sulfone (44) and its corresponding sulfide (45) showed the highest activity[174-177]. Compound 44 was highly effective in removing >90% H.nana worms from mice and rats at a dose of 10 and 100 mg/kg respectively, its maximum tolerated dose in mice was found to be > 2.7 g/kg[174,175]. Further studies on this compound indicated that it was also effective against Taenia species, D.caninum and Raillietina species at an oral dose of 50-100 mg/kg[176]. 4,4'-Diisothiocyanatodiphenyl sulfide (45) exhibited marked activity against H.nana in mice and rats at a dose of

50 mg/kg; its maximum tolerated dose was 2.7 g/kg[174-177].



44, X = SO_2

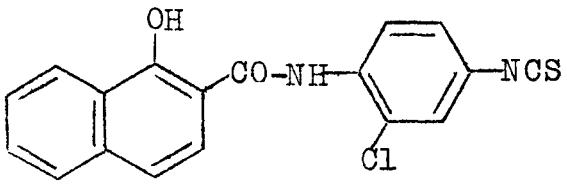
45, X = S

Based on the powerful cestodicidal activity of niclosamide and 44, a series of halogenated isothiocyanatosalicylanilides were synthesized possessing potent activity against H.nana in rats[162,164,165]. The best compound of this class was 3,5-dibromo-2'-chloro-4'-isothiocyanatosalicylanilide (42) which displayed high order of activity against a number of nematodes and cestodes in different hosts. At a dose of 100 mg/kg, it caused 100% elimination of H.nana in mice and rats and H.diminuta in Mastomys natalensis and also provided 100% cure rates except for H.nana in mice where the cure rate was 82%. In this test the drug was found to be better than niclosamide but inferior to praziquantel[166].

In an expanded study 42 was evaluated against a number of nematode and cestode parasites. It removed 100% of H.nana from mice and rats, Raillietina species from fowls and Taenia species from cats at a dose of 25-70 mg/kg. It was equally effective against Ancylostoma ceylanicum in hamsters, Syphacia obvelata in mice, Ascaridia galli in fowls,

Toxascaris species, Toxocara species, Ancylostoma tubaeformis and Gnathostoma spinigerum in cats and A.ceylanicum and T.canis in dogs at a dose ranging from 25-50 mg/kg given for 1-3 days[167].

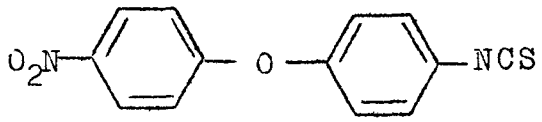
Some of the isothiocyanatonaphthanilides have also been found to possess high order of activity against different cestodes[178-180]. The most potent member of this class was 46 which resulted in 100% elimination of H.nana in rats at an oral dose of 7.5 mg/kg[178]. It also showed high activity against H.diminuta in rats and Taenia species in dogs. A single oral dose of 5 g/kg of this compound was well tolerated by rats. It was equally safe when given to mice, Mastomys and dogs.



46

The oxygen analog of amoscanate (47, Nitroscanate, GS-23654) has been found to possess high antitapeworm activity in dogs. At a dose of 1 g/kg or 250 mg/kg x 2, it eliminated all Echinococcus granulosus while a dose of 64 mg/kg of the drug was sufficient to remove T.hydatigena from dogs[181]. In another experiment against E.granulosus in dogs, nitroscanate was given as 25% suspension at a dose of 100,200 and 400 mg/kg divided in 1-3 doses, when three

doses of 400 mg/kg removed 92.6% of the tapeworms. The lower doses were less active[182].



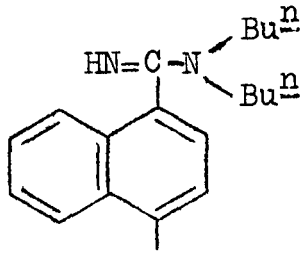
47

Substituted Amidines

In 1965, Wellcome laboratories reported the anthelmintic activity of a series of substituted naphthamidines of which N,N-dibutyl-4-n-hexyloxy-1-naphthamidine (48, Bunamidine) was found to exhibit the most potent taenicidal activity[183]. Since then bunamidine has been used extensively to treat various cestode infections in dogs, cats, sheep and poultry. Although this drug is too toxic for humans, it may be successfully used to prevent man from hydatid disease by eliminating Echinococcus reservoirs from cats and dogs.

At a dose of 15-40 mg/kg, bunamidine hydrochloride caused 90-100% clearance of Dipylidium from cats and dogs[184-187]. Treatment of sheep infected with M.expansa needed 12.5 mg/kg of the drug for lighter infections while a dose of 25-50 mg/kg of it was required for eliminating heavier infections[188]. Bunamidine was also highly effective in eliminating majority of T.pisiformis, H.taeniaeformis

and M.multiceps from cats and dogs at a dose of 25-50 mg (base)/kg. The drug showed differential response against American and English strains of T.pisiformis[184-186]. The efficacy of various salts of bunamidine has been demonstrated against R.cesticillus, R.tetragona and R.echinobothrida in chickens[189].



48

Benzimidazoles

Mebendazole (12) was given to 31 patients infected with T.solium and T.saginata at a dose of 100 mg twice daily for 2 days or at 200 mg twice daily for 4 days when 20, 72.7, and 90% cure rates were obtained[190]. In another clinical trials carried out in Costa Rica, 37 patients with T.solium and 4 patients with T.saginata infections were treated by mebendazole at a dose of 100-300 mg given twice daily for 2-6 days. This treatment removed long chains of proglottids from several patients 24-48 hours after drug administration and only fewer side effects were noticed[191].

Mebendazole was equally effective in removing tapeworms from pets. At a dose of 1 g given daily for 14 days, it killed both mature and immature cysticerci of

of T.pisiformis in rabbits[192]. It has been used to treat Uncinaria stenocephala, T.pisiformis and D.caninum infections in dogs at a dose of 100 mg given twice for 5 days[193]. The cysts of T.hydatigena and T.ovis in sheep were killed by mebendazole when given at a dose of 50 mg/kg given for 14 consecutive days[194].

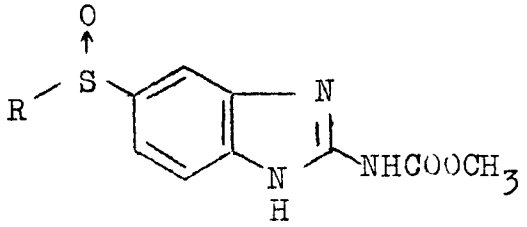
Fenbendazole (14) has been found effective in eliminating H.diminuta from rats and M.expansa from sheep and cattle at a dose of 10-25 mg/kg[195,196] and other tapeworms from domestic animals[197-199].

Oxfendazole (15) has been used to treat dogs infected with Echinococcus granulosus and T.hydatigena and sheep carrying Moniezia at a dose of 4.5-20 mg/kg when the animals were cured considerably[200-202].

Albendazole (16) shows high activity in removing Moniezia from sheep at a dose of 10 mg/kg[203,204] and T.saginata from calves at a dose of 45-50 mg/kg[205,206]. It also caused complete eradication of natural infections of M.expansa and M.benedeni from sheep at a dose of 10-20 mg/kg[205] and was highly effective against Mesocestoides corti in dogs[206].

Squibb laboratories have developed two injectable benzimidazoles, [5-[(cyclopropylmethyl)sulfinyl]-1H-benzimidazol-2-yl]carbamic acid methyl ester (49) and

[5-[(2-methylpropyl)sulfinyl]-1H-benzimidazol-2-yl]carbamic acid methyl ester (50) to treat nematode and cestode infections. A single s.c. injection of 49 given at a dose of 5 mg/kg removed 100% of Moniezia from naturally infected sheep. It was equally effective against Moniezia sp. at an oral dose of 2.5 mg/kg[207].



49, R = 

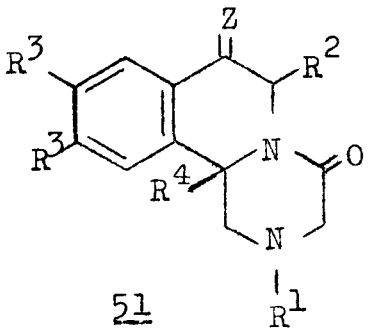
50, R = 

Praziquantel

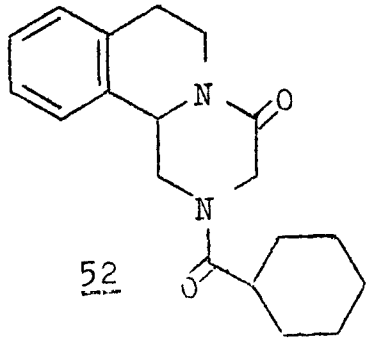
A large number of pyrazino-isoquinolines (51) have been synthesized jointly by Merck and Bayer laboratories which show high activity against H.nana in mice at a minimum inhibitory concentrations of 25-50 mg/kg[208-211]. From this series, 2-cyclohexylcarbonyl-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one (52; EMBAY 8440, Biltricide, Praziquantel) emerged as the most potent anthelmintic[212-214]. Praziquantel possesses high activity against the blood flukes Schistosoma haematobium, S.japonicum, S.mansoni and S.intercalatum[215-217] and cestode parasites in man and animals[218,219]. Recently the physical, chemical and biological properties of praziquantel has been published[220].

At a dose of 2.5 mg/kg, praziquantel eliminated all

T.hydatigena from dogs and Hydatigera taeniaeformis from cats[221]. However, a dose of 1 mg/kg of the drug was sufficient to remove all the worms of T.pisiformis and T.taeniaeformis from dogs and cats respectively[222]. Hamsters infected with D.latum showed high response when treated with praziquantel using at a dose of 50 mg/kg[223].



51



52

2.2 The Hydatid Disease

The hydatid disease, prevalent wherever man is closely associated with dogs, sheep and cats, is one of the most serious and fatal infection caused by cestodes. The disease is acquired by ingestion of eggs of Echinococcus granulosus and E.multilocularis. The definite hosts for these cestodes are the canine animals such as dogs, wolves, foxes, jackals and cats who harbour the adults worms in their small intestines. The intermediate hosts are man, sheep, cattle, dogs and camels.

The hydatid diseases generally do not show any symptom at the early stage, however various clinical manifestations such as nausea, vague abdominal pain, bulging of the right hypochondium or epigastrium due to hepatic enlargement and recurrent pyrexia associated with coughing paroxysms may occur which depend upon the size, type and site of the cysts. Sometimes the cyst may rupture due to some reasons which may give rise to anaphylactic shock with vasomotor collapse, oedema, utricaria and respiratory discomfort.

2.21 Treatment of hydatid infections

Arecoline hydrobromide (30) has been used since long to treat dogs infected with Echinococcus. At a dose of 4 mg/kg, arecoline HBr or HCl gives 95-98% efficacy against E.granulosus in dogs[224,225].

Bithionol (34) and its corresponding sulfoxide have been recommended for treating dogs carrying E.multilocularis infection and give high cure rates at 150 and 200 mg/kg respectively[226].

Niclosamide (35) shows variable activity against E.granulosus[227,228], however at a single oral dose of 50 and 100 mg/kg it removed 50% and 98-100% of these tapeworms from dogs[229].

Bunamidine (48) is the most extensively used drug against E.granulosus in dogs and sheep and is generally employed as its hydrochloride or hydroxynaphthoate. The drug is generally given in two doses at 24 or 48 hours intervals[230-232]. Bunamidine hydrochloride removed 90-94% of E.granulosus worms from several dogs at a single dose of 50 mg/kg[233,234], while at a dose of 25 mg/kg, 50 mg/kg or 25 mg/kg given twice at 48 hour intervals resulted in 98.8, 85.9, and 98.5% reduction of E.granulosus respectively in 12 dogs[235]. In some countries dogs and sheep with potential exposure of E.granulosus infections were treated biweekly (with 100 mg/kg) or monthly (with 25 mg/kg) by bunamidine for a long period resulting in sharp fall in hydatid infections. No toxic symptoms developed even the animals were treated for several years[236,237]. Bunamidine hydrochloride is also effective against E.multilocularis in dogs at a dose of 40 mg/kg[226].

Bunamidine hydroxynaphthoate, at a single oral dose of 100 mg/kg cleared 97% of E.granulosus infection from 12 of 15 dogs[238].

Mebendazole (12) is another recent drug which has been found to exhibit high activity against E.granulosus at a single or multiple dose of 1.25-160 mg/kg causing significant reduction of parasites in different animals[239-241].

Mebendazole, given intraperitoneally at 75-150 mg/kg daily for 3 days, was 95-100% effective against E.multilocularis[241].

Praziquantel (52) is the latest drug introduced to treat hydatid diseases in dogs, cats and sheep with high success. It is 100% effective against E.granulosus[242,243] and E.multilocularis[244] at a dose of 5 mg/kg.

3. Conclusion

It is evident from the present survey that a number of broad-spectrum anthelmintics have been developed replacing old traditional drugs which can be used successfully to eradicate various gastrointestinal helminths from both man and domestic animals. However, keeping in view the high rate of incidence of intestinal helminthiasis disease, risk of reinfection and lack of long-effective drugs, the search for newer chemotherapeutic agents still continues. There is ample scope to develop longer-acting drugs effective on immature, mature and cystic forms of the worms. Synthesis of large number of compounds based on emperical and semi-emperical approach and evaluation of their anthelmintic efficacy and detailed SAR of potent drug series would help in enlightening newer avenues.

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Chapter II

SYNTHESIS OF POTENTIAL NEMATODICIDAL AND CESTODICIDAL AGENTS

1. INTRODUCTION:

In 1947, when Stoll[1] presented a world-wide survey of various helminth infestations in man, it was found that the number of subjects suffering from different intestinal helminths was nearly 2000 million*. This may be attributed probably due to lack of suitable drugs and inadequate knowledge of various aspects of the disease at that time. Since then, more than three decades have passed but the number of cases with intestinal nematode and cestode infections does not seem to have declined despite several measures taken to eliminate helminthiasis from masses. It is estimated that more than 2500 million people suffer from different forms of intestinal nematode infections[2,3] while more than 870 million people carry the cestode parasites[2,4].

Although the poor sanitary habits, lack of prophylaxis and prevalence of proper natural conditions for development of helminth juveniles are the main criterions for the overwhelming increase in the incidence of intestinal helminthiasis, the non-availability of an ideal anthelmintic to masses is also an important factor. An ideal anthelmintic

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*Values indicate sum of the patients infected with different nematode and cestode parasites.

for intestinal helminthiasis should be safe and have broader spectrum of activity which could be used effectively to eradicate both nematodes and cestodes, if co-existing, from the gastrointestinal tract. Such type of an anthelmintic would certainly play a vital role in the treatment of such diseases because of the high concurrence of multiple helminth infections in several tropical and sub-tropical regions of the world.

Since last fifteen years, a good progress has been made in the chemotherapy of intestinal helminthiasis. In addition, a more detailed study has been carried out directed towards the biochemistry of the helminth parasites, host-parasite relationships and mode of action of several known anthelmintics. This has greatly helped in providing better treatment of this disease in humans. The evolution of powerful anthelmintics derived from benzimidazoles, arylisothiocyanates and imidazolines has successfully eliminated several bottle-necks (such as toxicity and selective action of classical drugs) in the chemotherapy of man and domestic animals[5]. However, the final answer to the problem has not yet been achieved. It is in this context that the pursuit to find better chemotherapeutic agents for the treatment of intestinal helminthiasis still continues.

2. BASIS OF WORK:

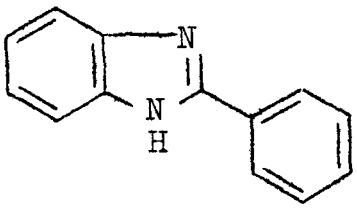
One of the most remarkable achievements in the modern chemotherapy of helminthiasis has been the recognition of benzimidazole nucleus as a useful pharmacophore for the synthesis of potent antinematode drugs[6]. This has resulted in the discovery of a series of benzimidazole anthelmintics possessing powerful activity against different helminth parasites in man and animals. 2-Phenylbenzimidazole (1, phenzidole)[7] is the first member of this series which has been used to treat animal helminthiasis in early 60's in combination with phenothiazine. Substitution of the phenyl residue in phenzidole by a 4-thiazolyl moiety gave thiabendazole (2) which proved to be a highly successful drug in the treatment of hookworm infections, creeping eruption and also showed antiinflammatory activity[8]. The discovery of this broad spectrum anthelmintic stimulated research in the benzimidazole anthelmintics in various laboratories of the world. The efforts resulted in the synthesis of cambendazole (3), another congener of thiabendazole, with potent anthelmintic action, carrying a 4-thiazolyl and i-propoxycarbonylamino function at 2 and 5-positions respectively of benzimidazole ring[8].

The substitution of aryl and heteroaryl group by a carbalkoxyamino function at 2-position of benzimidazole proved to be highly fruitful as several compounds (4-11) were shown to possess high cure rates against various human and animal helminth infections[8]. The most active compounds of this series are mebendazole (5) and fenbendazole (7) which showed great promise in chemotherapy of human and animal intestinal nematodes.

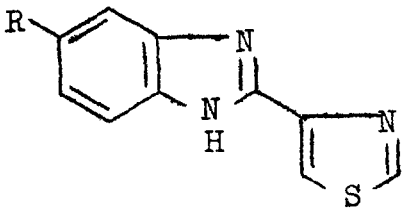
Some of arylisothiocyanates such as phenylisothiocyanate (12)[9] and 1,4-phenylenediisothiocyanate (13, bitoscanate)[10] are highly effective in eliminating hookworm infestations from different hosts including humans.

Several diaryl sulfides and sulfones have also been shown to exhibit high cestodicidal activity from this laboratory. The most active compounds of this series are 1,4-diisothiocyanatodiphenyl sulfide(14) and sulfone (15)[11].

Although several drugs have emerged possessing high activity against different human and animal helminth parasites, none can be an ideal as most of them either possess low therapeutic indices or if safe do not eliminate all the gastrointestinal nematodes and cestodes since mixed helminth infection is a common and concurrent

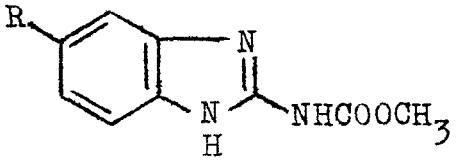


1, (Phenzidole)



2, R = H (Thiabendazole)

3, R = NHCOOPr^{i}, (Cambendazole)



4, R = Bu^{n}, (Parbendazole)

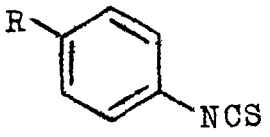
5, R = COPh (Mebendazole)

6, R = OPr (Oxibendazole)

7, R = SPh (Fenbendazole)

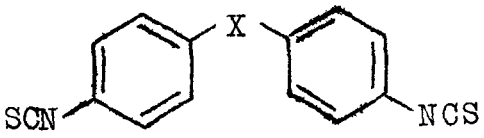
8, R = SOPh (Oxfendazole)

9, R = SPr (Albendazole)



12, R = H

13, R = NCS (Bitoscanate)

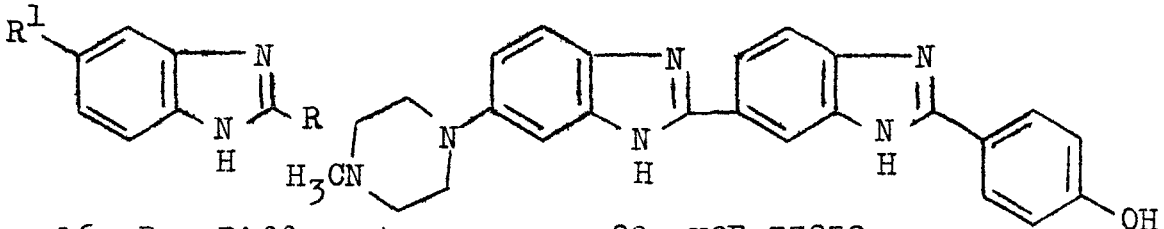


14, X = S

15, X = SO_2

10, R = $COC_6H_4F(p)$ (Flubendazole)

11, R = CO-  (Ciclobendazole)



16, R = Different substituents

R^1 = N-acyl and N-aroyl group

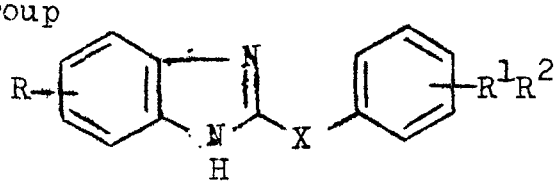
17, R = CF_3, R^1 = H

18, R = H,

R^1 = Substituted phenyl

19, R = H, R^1 = NO_2

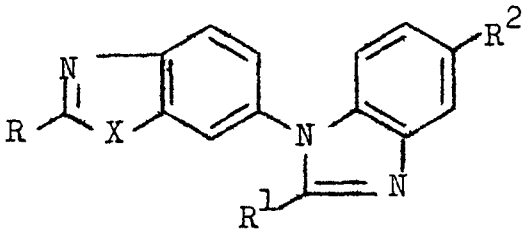
20, HOE-33258



21, X = S, SO_2

problem in several developing countries of the world. Hence, the need to develop new compounds possessing all the requirements of an ideal drug can not be overlooked.

Keeping in view, the versatality of benzimidazole nucleus in building molecules with wide-spectrum of biological activity, it was considered rational to synthesize various N-heteroarylbenzimidazoles and benzthiazoles of the type I, II* with an aim to enhance the

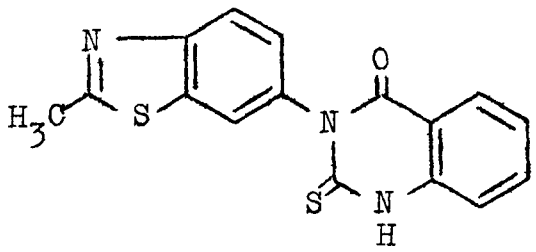


I, R = CH_3, H

X = NH, S

R^1= CH_3, H, NHCOOEt, SH

R^2= NCS, $NHCOCH_3$, NHCOH



II

biological profile of benzimidazoles as also to map out the minimal structural requirements for optimal activity. The synthesis of I and II was also supported by the fact that several 5(6)-acyl, aroylamino, 5-substituted phenyl and 2-trifluoromethylbenzimidazoles (16-19)[12-17] show

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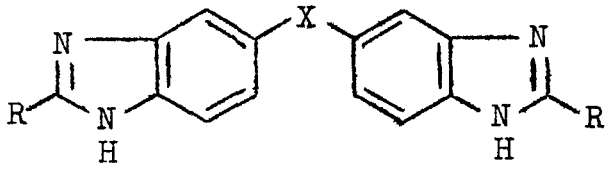
*All the prototype molecules have been denoted in Roman numbers while the de facto compounds synthesized are given in Arabic numbers.

marked anthelmintic activity (Scheme 1-3).*

The powerful anthelmintic activity exhibited by several alkyl 5(6)-substituted benzimidazole-2-carbamates (4-11)[8], some of which even used to treat human helminthiasis, is thought to be due to an appropriate substituent at 5(6)-position and carbamate moiety at 2-position of benzimidazole ring. Maintaining these minimal structural requirements it was considered of interest to synthesize a series of di-benzimidazoles of the type III with different substituents at 2,2'-positions. This work was carried out to study the role of benzimidazole ring as a carrier molecule in yielding high biological activity and also to establish the structure-activity relationship in 2,5-disubstituted benzimidazoles (Scheme 4-11).



III, R = H, CH_3, $NHCOOCH_3$, NHCOOEt

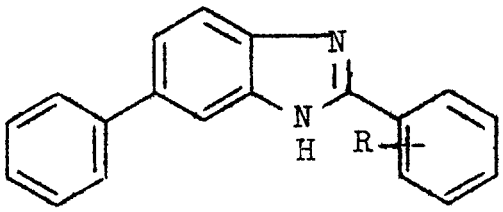
X = S, SO_2, CO, CH_2, O,

$-SCH_2CH_2S-$, 

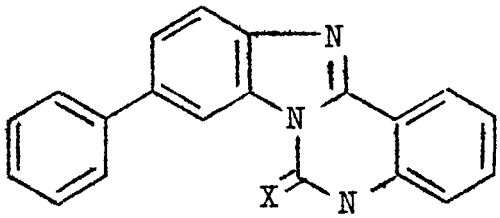
Although, a large number of 2-arylbenzimidazoles such as phenzidole[7], thiabendazole[8], cambendazole[8], HOE-33258 (20)[18] have been shown to exhibit powerful anthelmintic action in human and animals, a detailed study

*Discussed in Sec.3.

directed towards exploring the biological potential of various 2-arylbenzimidazoles is still lacking[8]. Hence, it was proposed to synthesize a series of 5(6)-phenyl-2-substituted arylbenzimidazoles and their cyclic analogs of the type IV, V (Scheme 12).



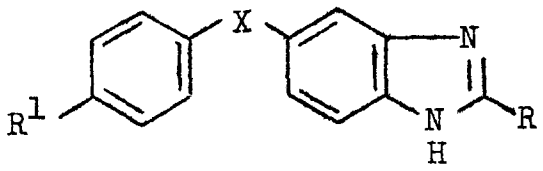
IV, R = 2-NH_2, 4-NH_2, 4-NCS
4-NHCOOEt, 4-$NHCOOCH_3$



V, X = O, S

The demonstration of high cestodicidal activity[11] of 4,4'-diisothiocyanatodiphenyl sulfide (14) and 4,4'-diisothiocyanatodiphenyl sulfone (15)[11] has established a definite role of sulfide and sulfone linkage in helminth chemotherapy. This fact was further supported by introduction of fenbendazole (7)[8] as a broad spectrum anthelmintic and 2-arylthio and sulfono benzimidazoles (21) reported by earlier workers in this laboratory with high cestodicidal activity[19]. These observations led us to synthesize various substituted diaryl sulfides and sulfones and their related compounds of the type VI where one of the aryls of 14 and 15 has been replaced by more versatile benzimidazole pharmacophore and to

evaluate their biological activities (Scheme 13 and 14).

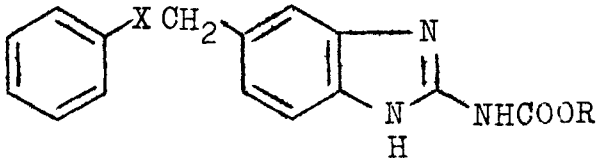


VI, R = H, CH_3, $NHCOOCH_3$, NHCOOEt

X = S, SO_2, O

R^1 = NHAc, NH_2, NCS

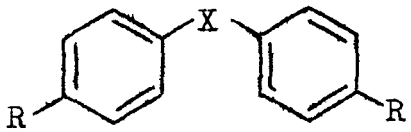
Synthesis of higher homolog of fenbendazole (7)[8] and its oxygen analog was also undertaken in order to evaluate the change in its biological activity by introduction of a CH_2 unit at 5-position of benzimidazole ring (VII) (Scheme 15).



VII, R = CH_3, C_2H_5, X = O, S

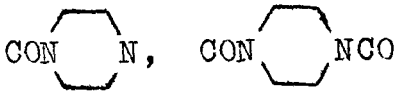
The high cestodicidal activity of 14 and 15 prompted us for a further probe in this direction. Hence, few more diisothiocyanatodiaryl sulfides and sulfones of the type VIII were prepared and evaluated for their cestodicidal activity where the distance between two arylthio and sulfono functions is increased by introduction of two or three CH_2 units. Some other active pharmacophores such

as 1,4-dicarbonylpiperazine and 1-carbonylpiperazine have also been introduced between two phenyl rings (VIII) and the change in activity was studied (Scheme 16, and 20).

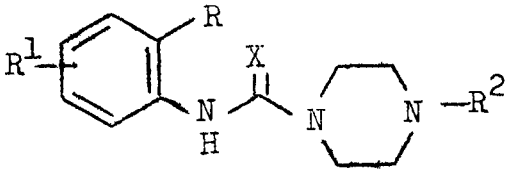


VIII, R = NHAc, NH_2, NO_2, NCS

X = $S(CH_2)_nS$, $SO_2(CH_2)_nSO_2$, n = 2,3



Despite 1,4-phenylenediisothiocyanate (13, bitoscanate) has been used to treat various hookworm infections[10], it has some serious side effects and is also toxic to animals. Hence its clinical acceptibility is still doubtful and conflicting views have been reported[20]. This led us to carry out some structural changes in the parent molecule by introduction of either piperazine or benzimidazole residues, which are accepted pharmacophores in antinematode drugs, on either side of isothiocyanato function. This is in conjunction with the facts that some of the arylthioureas and ureas show marked anthelmintic activity[21,22]. Thus, the compounds of the types IX-XI were synthesized and screened for their antihookworm activity (Scheme 17 and 18).

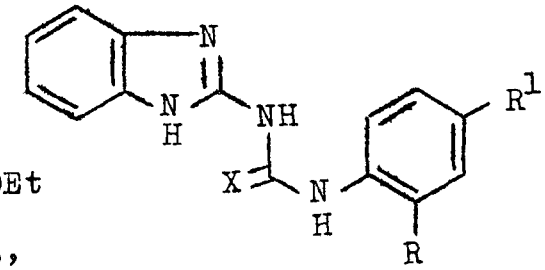


IX, R^2 = CH_3, CH_2Ph, Ph, COOEt

R^1 = 3-NO_2, 4-NO_2, 4-NH_2, 4-NCS

R = H, Cl

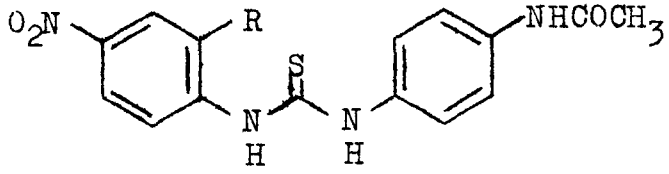
X = S, O



X, R^1 = NO_2, NH_2, NCS

R = H, Cl

X = S, O



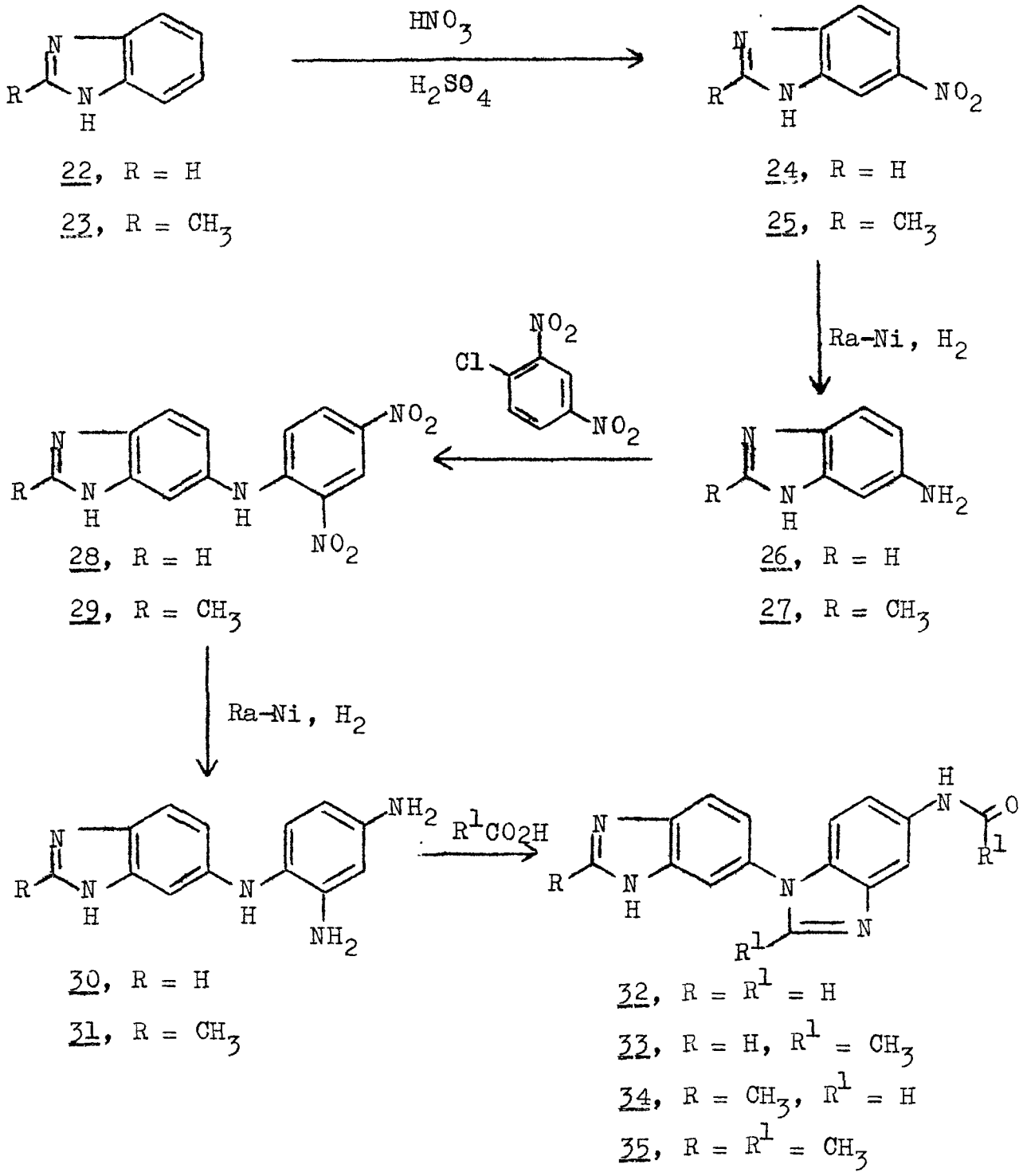
XI, R = H, Cl

During the reaction of thiocarboxamides, thioamide and thioureas with thiophosgene, the unusual desulphurization of these compounds was observed which was studied in detail by converting a number of thiocarboxamides, thioamide and thioureas into their corresponding carboxamides, amide and ureas. The mechanism of desulphurization has also been discussed (Scheme 19).

3. CHEMISTRY:

3.1 Synthesis of 2-substituted 5(6)-N-heteroarylbenzimidazoles

Benzimidazole (22) and 2-methylbenzimidazole (23), obtained by reaction of o-phenylenediamine with formic and acetic acids[23], were nitrated using HNO_3-H_2SO_4 mixture to give 5(6)-nitrobenzimidazole (24) and 2-methyl-5(6)-nitrobenzimidazole (25)[24]. Catalytic hydrogenation of 24 and 25 using Raney-nickel in a Paar hydrogenator afforded the respective 5(6)-aminobenzimidazoles (26 and 27)[25], which were condensed with 2,4-dinitrochlorobenzene in ethanol in presence of triethylamine to yield 5(6)-(2,4-dinitrophenyl)aminobenzimidazole (28) and 2-methyl-5(6)-(2,4-dinitrophenyl)aminobenzimidazole (29) respectively. Hydrogenation of 28 and 29 in presence of Raney-nickel catalyst gave the corresponding 5(6)-(2,4-diaminophenyl) aminobenzimidazoles (30 and 31). Better yields of 30 and 31 were obtained by reducing 28 and 29 with hydrazine-hydrate and Raney-nickel in ethanol-THF mixture. Cyclization of 30 and 31 with formic and acetic acids resulted in formation of 2-substituted-5(6)-(2,5-disubstituted-1-benzimidazolyl)benzimidazoles (32-35) (Scheme 1).



22, R = H

23, R = CH_3

24, R = H

25, R = CH_3

26, R = H

27, R = CH_3

28, R = H

29, R = CH_3

30, R = H

31, R = CH_3

32, R = R^1 = H

33, R = H, R^1 = CH_3

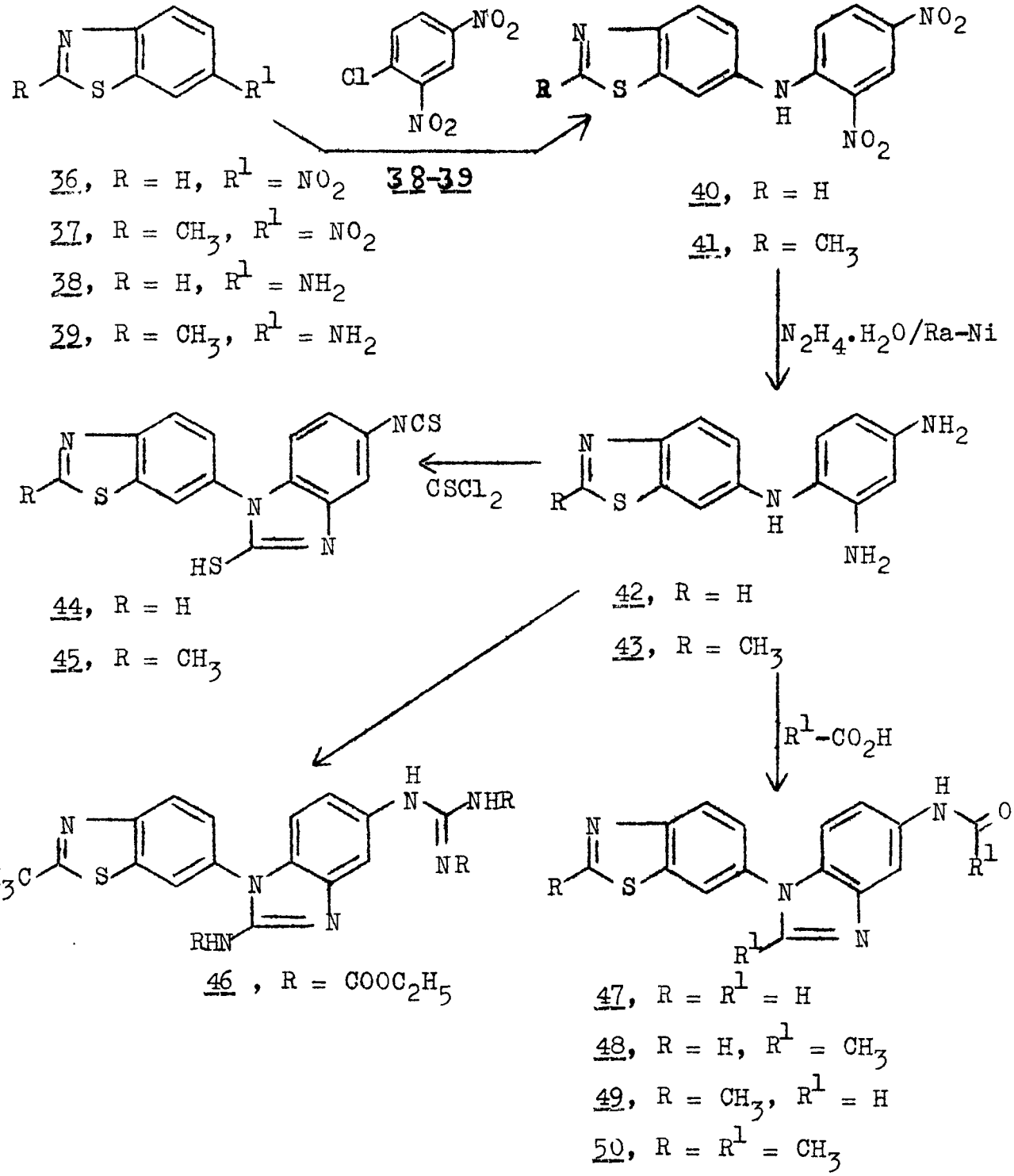
34, R = CH_3, R^1 = H

35, R = R^1 = CH_3

Scheme 1

3.2 Synthesis of 2-substituted 6-N-heteroaryl benzthiazoles

Nitration of benzthiazole[26] and 2-methylbenzthiazole[27] with HNO_3-H_2SO_4 mixture gave 6-nitrobenzthiazole (36) and 2-methyl-6-nitrobenzthiazole (37) respectively. Reduction of 36 with $SaCl_2$-HCl gave 6-aminobenzthiazole (38)[28]. However 6-amino-2-methylbenzthiazole (39) could not be prepared by literature method[27] but it was obtained in good yield by reduction of 37 with hydrazine-hydrate and Raney-nickel. Reaction of 38 and 39 with 2,4-dinitrochlorobenzene in ethanol in presence of triethylamine gave good yields of 6-(2,4-dinitrophenyl)aminobenzthiazole (40) and 2-methyl-6-(2,4-dinitrophenyl)aminobenzthiazole (41), which were reduced smoothly using freshly washed Raney-nickel and hydrazine-hydrate in ethanol-THF mixture to yield the corresponding 2-substituted-6-(2,4-diaminophenyl)aminobenzthiazoles (42 and 43). Treatment of 42 and 43 with thiophosgene in acetone afforded 2-substituted-6-(2-mercapto-5-isothiocyanato-1-benzimidazolyl)benzthiazoles (44 and 45). The cyclization of 42 and 43 was carried out by treating with formic and acetic acids to yield directly 2-substituted-6-(2,5-disubstituted-1-benzimidazolyl)benzthiazoles (47-50). A similar cyclization of 43 with 1,3-dicarbethoxy-S-methylisothiourea in ethanol gave 2-methyl-6-[2-carbethoxyamino-5-(N,N'-dicarbethoxyguanidino)-1-benzimidazolyl]benzthiazole (46) in poor yield (Scheme 2).

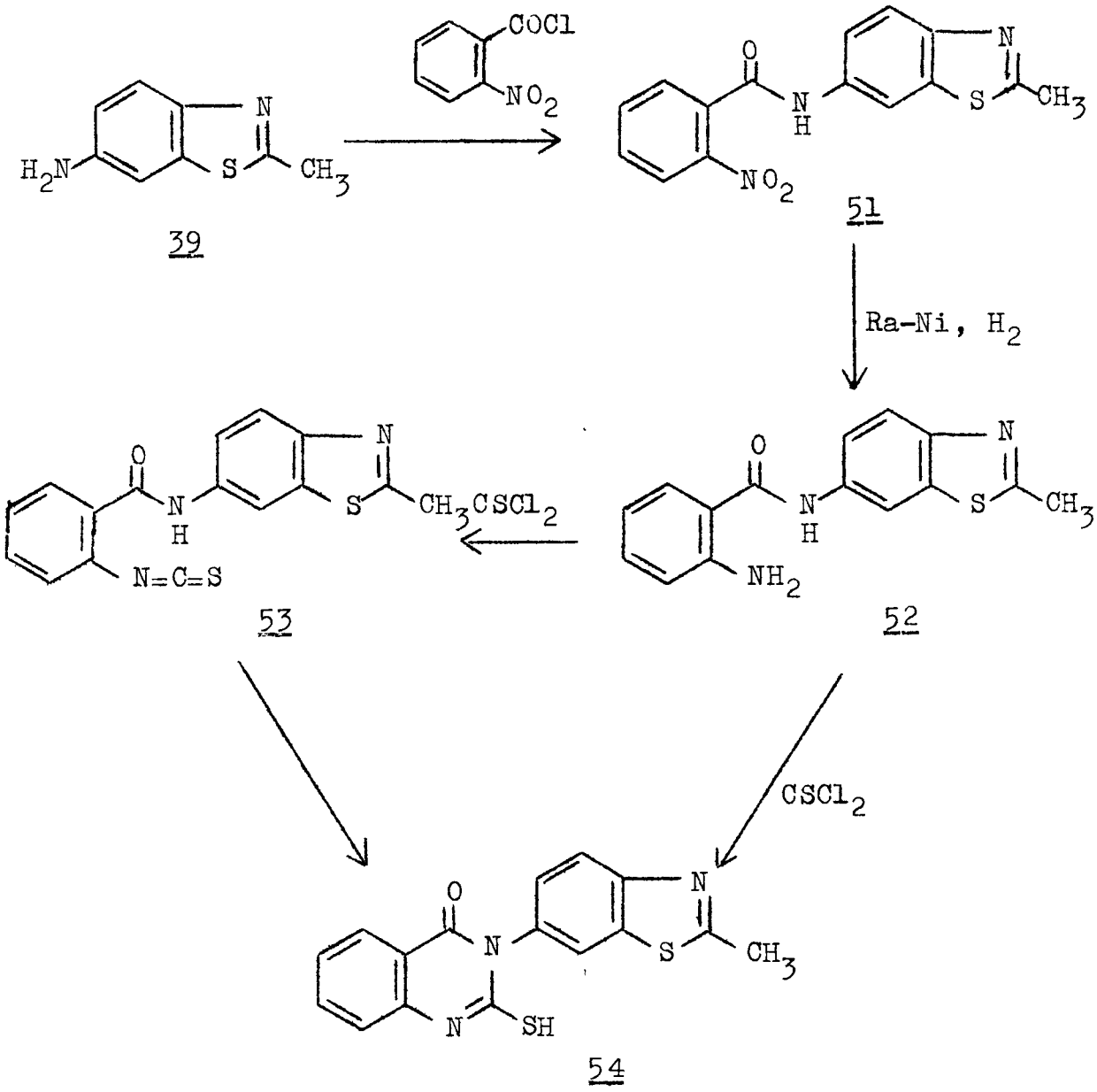

36, R = H, R1 = NO2
37, R = CH3, R1 = NO2
38, R = H, R1 = NH2
39, R = CH3, R1 = NH2
38-39
40, R = H
41, R = CH3
N2H4.H2O/Ra-Ni
42, R = H
43, R = CH3
CSCl2
44, R = H
45, R = CH3
R1-CO2H
46, R = COOC2H5
47, R = R1 = H
48, R = H, R1 = CH3
49, R = CH3, R1 = H
50, R = R1 = CH3

Scheme 2

Reaction of 39 with 2-nitrobenzoylchloride in presence of triethylamine afforded 2-methyl-6-(2-nitrobenzoyl)aminobenzthiazole (51) which was reduced using Raney-nickel and hydrogen in a Paar hydrogenator to give 2-methyl-6-(2-aminobenzoyl)aminobenzthiazole (52). Reaction of 52 with thiophosgene in acetic acid-HCl-chloroform mixture afforded the isothiocyanate 53 in poor yield which was converted thermally into 2-methyl-6-(2-thioxo-4-oxo-3-quinazolinyl) benzthiazole (54). The latter was also prepared by reaction of 52 with one mole of thiophosgene (Scheme 3).

3.3 Synthesis of 2,2'-substituted-5,5'-dibenzimidazolyl derivatives

m-Chloroacetanilide (55), obtained by acetylation of m-chloroaniline using AcOH-Ac_2O, was nitrated[29] with acetic acid-nitric acid mixture to give 5-chloro-2-nitroacetanilide (56). Reaction of 56 with sodium sulfide in ethanol yielded the deacetylated sulfide 3,3'-diamino-4,4'-dinitrodiphenyl sulfide (57). It's structure was confirmed by NMR of its acetyl derivative 3,3'-diacetamido-4,4'-dinitrodiphenyl sulfide (58) obtained by acetylation of 57 with AcOH-Ac_2O mixture. Reduction of 57 with ferrous sulphate-ammonia in acetone gave 3,3',4,4'-tetraaminodiphenyl sulfide (59). Since this amine (59) was highly susceptible to aerial oxidation it was immediately treated with formic



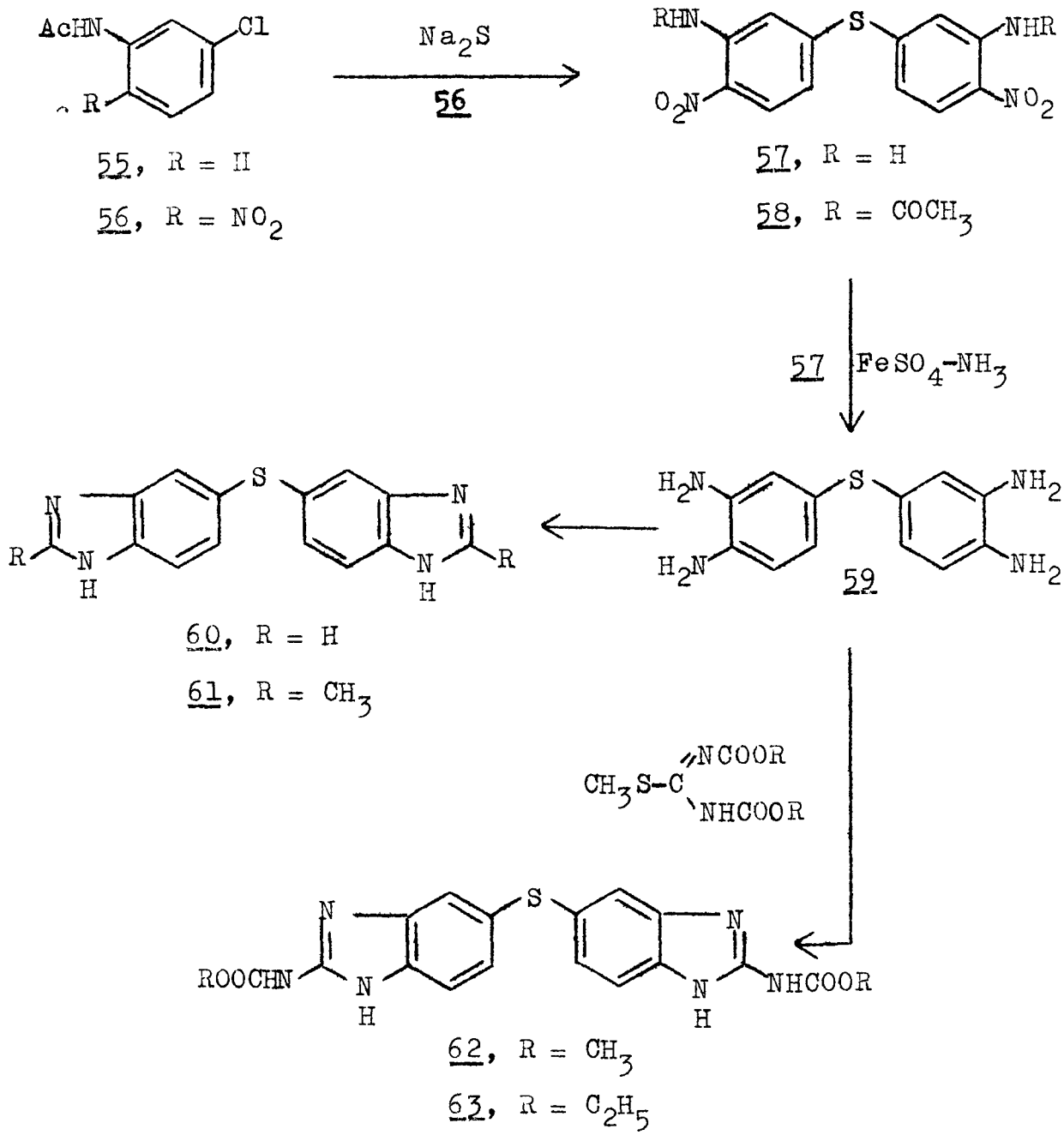
39 51 52 53 54

Scheme 3

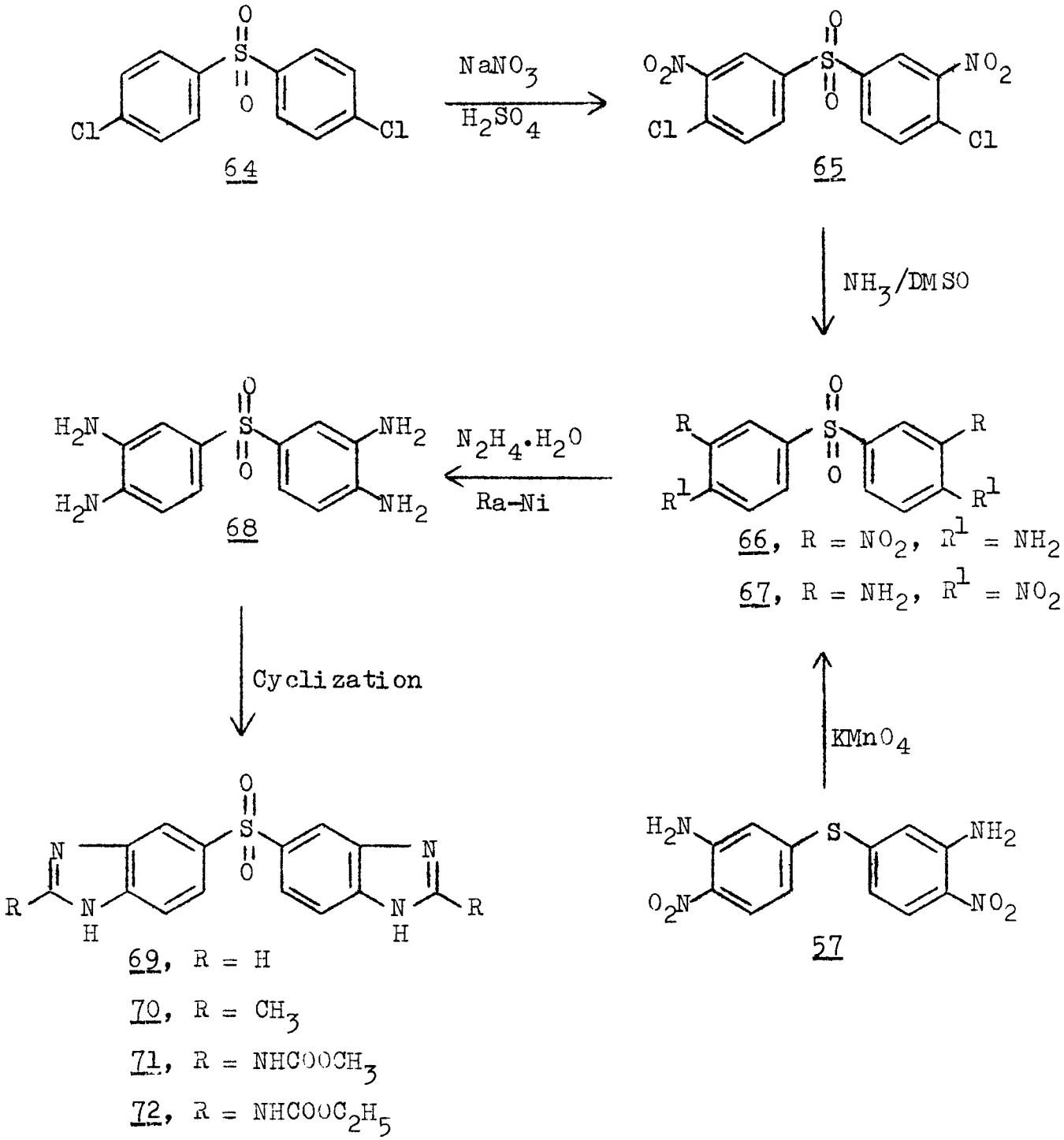
and acetic acids at their refluxing temperatures to afford the corresponding dibenzimidazoles (60-61). Reaction of 59 with 1,3-dicarbalkoxy-S-methylisothioureas in ethanol gave 2,2'-dicarbalkoxyamino-5,5'-dibenzimidazolyl sulfides (62 and 63) (Scheme 4).

4,4'-Dichlorodiphenyl sulfone (64) was nitrated with HNO_3-H_2SO_4 to afford 4,4'-dichloro-3,3'-dinitrodiphenyl sulfone (65)[30] which was treated with ammonia in DMSO to give 4,4'-diamino-3,3'-dinitrodiphenyl sulfone (66)[31]. The positional isomer of 66, 3,3'-diamino-4,4'-dinitrodiphenyl sulfone (67) was obtained in poor yield by direct oxidation of 57 using $KMnO_4$ in 80% aqueous acetic acid. Reduction of 66 or 67 with hydrazine-hydrate and Raney-nickel in ethanol-THF mixture gave 3,3',4,4'-tetra-aminodiphenyl sulfone (68) which was allowed to react with formic and acetic acids to afford the 5,5'-dibenzimidazolyl sulfone (69) and 2,2'-dimethyl-5,5'-dibenzimidazolyl sulfone (70) respectively. Cyclization of 68 with 1,3-dicarbalkoxy-S-methylisothioureas in refluxing ethanol gave 2,2'-dicarbalkoxyamino-5,5'-dibenzimidazolyl sulfones (71 and 72) (Scheme 5).

4-Acetamidobenzoic acid (73), obtained by reduction and subsequent acetylation of 4-nitrobenzoic acid, was nitrated using fuming nitric acid to give 4-acetamido-3-nitrobenzoic acid (74)[32]. The hydrolysis of 74 in


AcHN
Cl
R
Na2S
56
RHN
S
NHR
O2N
NO2
55, R = H
56, R = NO2
57, R = H
58, R = COCH3
57
FeSO4-NH3
H2N
S
NH2
H2N
NH2
59
N
S
N
R
N
N
R
H
H
60, R = H
61, R = CH3
CH3S-C
NCOOR
NHCOOR
ROOCHN
N
S
N
N
NHCOOR
H
H
62, R = CH3
63, R = C2H5

Scheme 4



64

65

66, R = NO_2, R^1 = NH_2

67, R = NH_2, R^1 = NO_2

68

57

69, R = H

70, R = CH_3

71, R = $NHCOOCH_3$

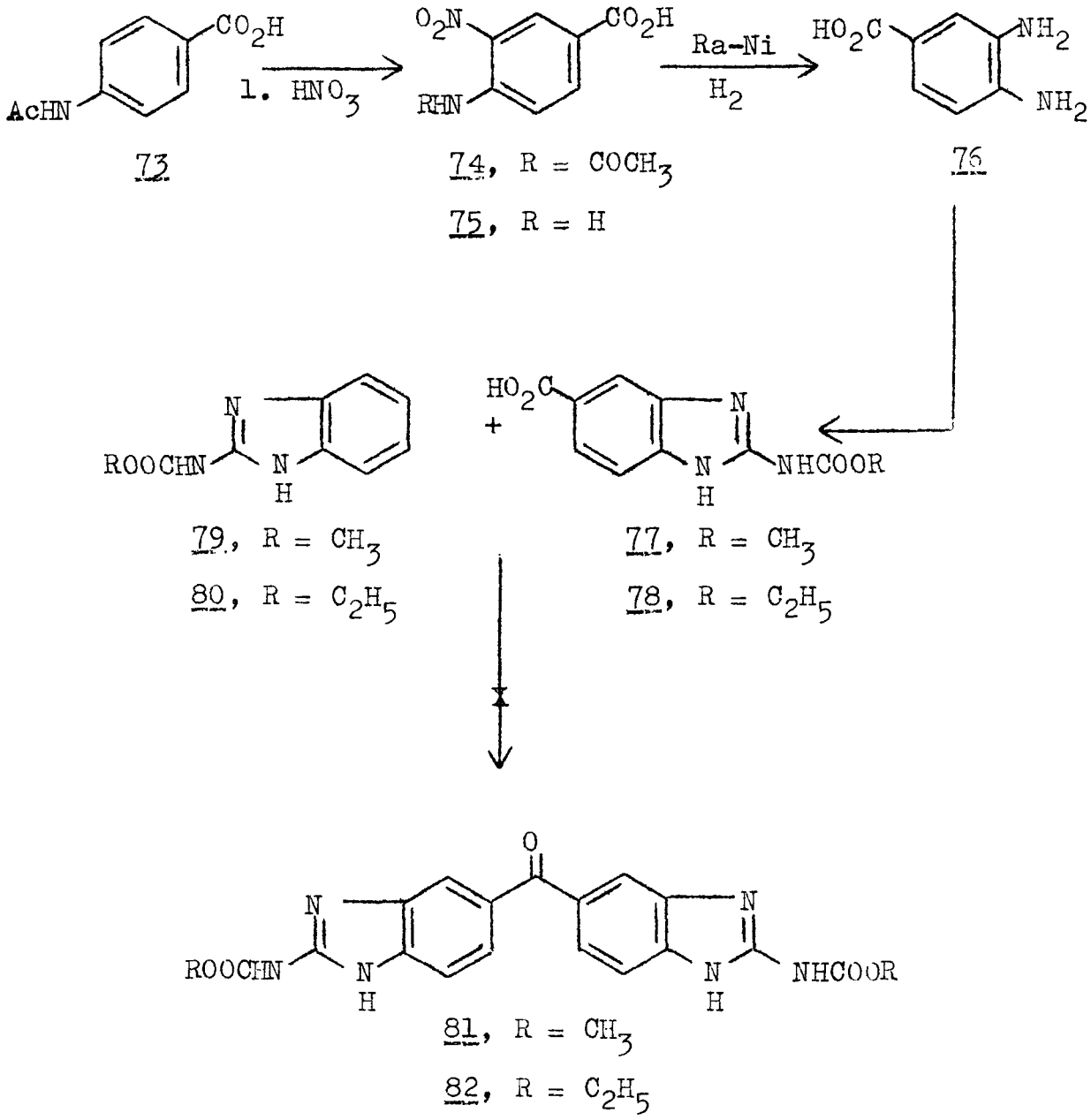
72, R = $NHCOOC_2H_5$

Scheme 5

concentrated HCl yielded 4-amino-3-nitrobenzoic acid (75)[32], which was reduced with Raney-nickel and H_2 in a Paar hydrogenator to give 3,4-diaminobenzoic acid (76)[33]. Reaction of 1,3-dicarbalkoxy-S-methylisothioureas with 76 afforded the corresponding 2-carbalkoxyaminobenzimidazole-5(6)-carboxylic acids (77 and 78).

Attempts to prepare 2,2'-dicarbalkoxyamino-5,5'-dibenzimidazolyl ketone (81 and 82) by Friedel-Crafts aroylation of alkyl benzimidazole-2-carbamates (79 and 80)[33a], obtained by cyclization of o-phenylenediamine with 1,3-dicarbalkoxy-S-methylisothioureas, with 77 and 78 did not work because of their poor solubility in different organic solvents.(Scheme 6).

In an alternative approach to prepare 81 and 82, 4,4'-dichlorobenzophenone (83), prepared from 4-chlorobenzoylchloride and chlorobenzene in CS_2 in presence of $AlCl_3$[34], was nitrated using H_2SO_4-HNO_3 to yield 3,3'-dinitro-4,4'-dichlorobenzophenone (84)[35]. Amination of 84 in DMSO at 140°C with ammonia gas afforded the corresponding 4,4'-diamino-3,3'-dinitrobenzophenone (85)[36] which was catalytically hydrogenated using Raney-nickel to give 3,3',4,4'-tetra-aminobenzophenone (86)[37]. Reaction of 86 with 1,3-dicarbalkoxy-S-methylisothioureas in refluxing ethanol yielded the title compounds (81 and 82) in good yields. The Wolff-Kishner reduction of 85 using



73

74, R = $COCH_3$

75, R = H

76

79, R = CH_3

80, R = C_2H_5

77, R = CH_3

78, R = C_2H_5

81, R = CH_3

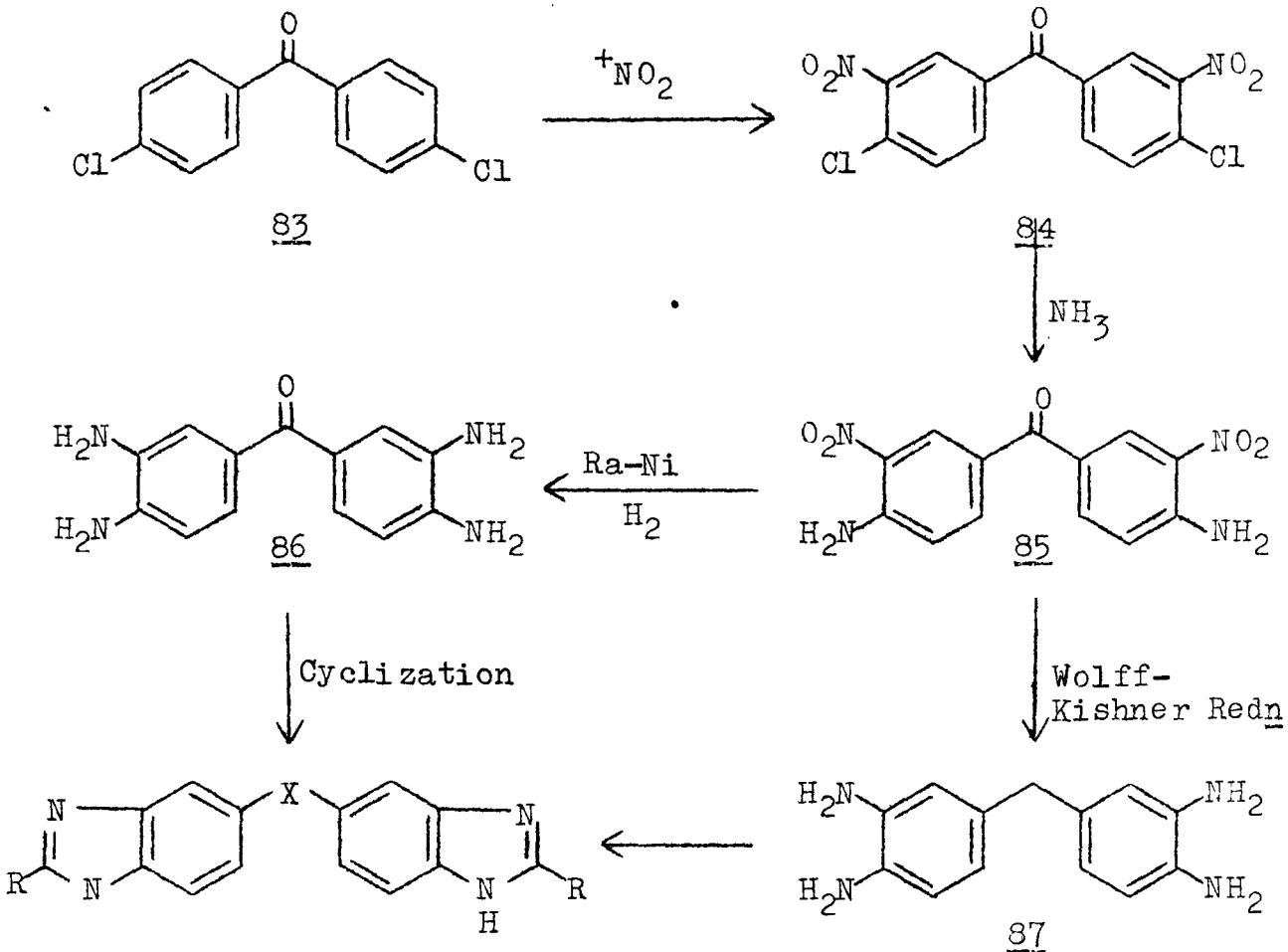
82, R = C_2H_5

Scheme 6

hydrazine-hydrate and potassium hydroxide in steel bomb at 170°C directly yielded the 3,3',4,4'-tetra-aminodiphenylmethane (87)[37] which was cyclized with 1,3-dicarbalkoxy-S-methylisothioureas in ethanol to give 2,2'-dicarbalkoxyamino-5,5'-dibenzimidazolylmethanes (90 and 91). Treatment of 86 and 87 with formic and glacial acetic acids afforded the corresponding 5,5'-dibenzimidazolyl ketones (88 and 89) and methanes (92 and 93) (Scheme 7).

Acetylation of 4-acetamidophenol (94) using pyridine-acetic anhydride gave 4-acetoxyacetanilide (95)[38], which was nitrated using fuming nitric acid to give 4-acetoxy-2-nitroacetanilide (96)[38]. Selective hydrolysis of 96 with aqueous KOH gave 3-nitro-4-acetamidophenol (97)[38] which when treated with 5-chloro-2-nitroaniline (98) and 5-chloro-2-nitroacetanilide (56) could not yield 99 and 100 under different experimental conditions. In another attempt, 4-acetamidophenol (94) was treated with 5-chloro-2-nitroacetanilide (56) to give 5-(4-acetamidophenoxy)-2-nitroacetanilide (101). Nitration of 101 under different experimental conditions also did not yield the required intermediate 100 which could have led to the formation of the compounds of the type III (X=O). (Scheme 8).

4,4'-Dinitrodiphenyl ether (102)[39], prepared from 4-nitrophenol and 1-chloro-4-nitrobenzene in presence of KOH in dry DMF, was reduced with hydrazine-hydrate and



81, R = $NHCOOCH_3$, X = CO

82, R = $NHCOOC_2H_5$, X = CO

88, R = H, X = CO

89, R = CH_3, X = CO

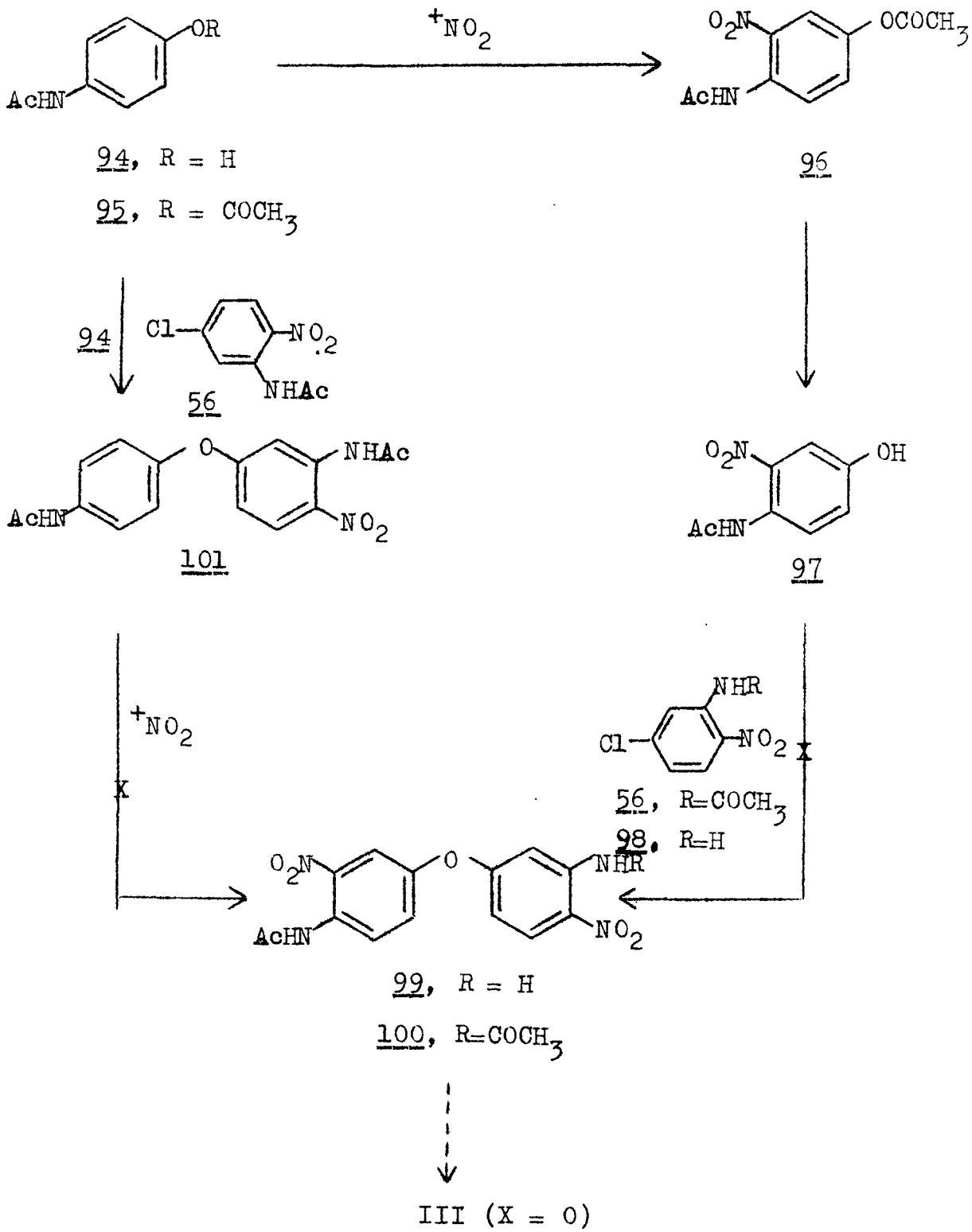
90, R = $NHCOOCH_3$, X = CH_2

91, R = $NHCOOC_2H_5$, X = CH_2

92, R = H, X = CH_2

93, R = CH_3, X = CH_2

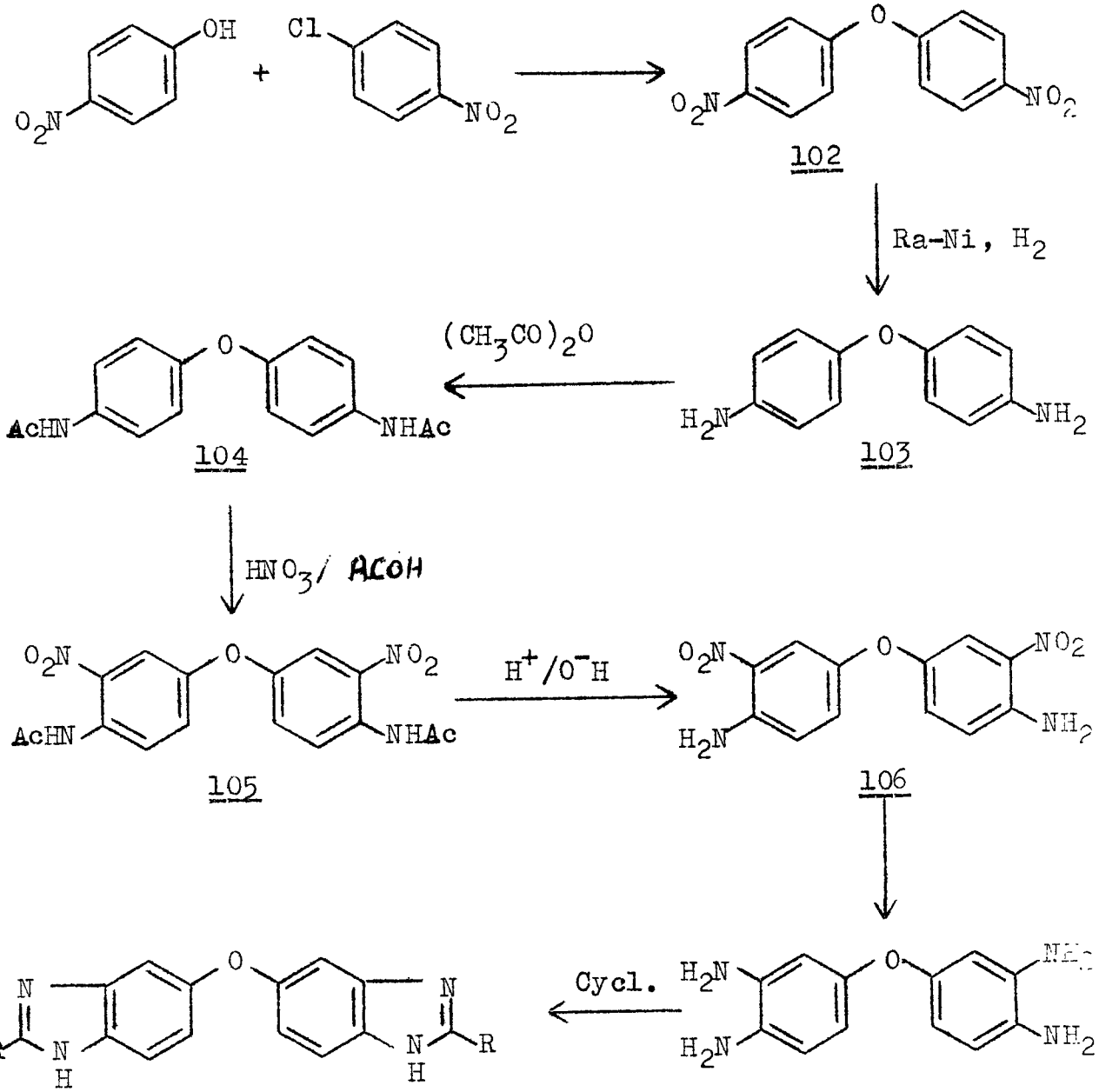
Scheme 7


OR
AcHN
+NO2
O2N
OCOCH3
AcHN
94, R = H
95, R = COCH3
96
94
Cl
NO2
NHAc
56
O
NHAc
AcHN
NO2
101
O2N
OH
AcHN
97
+NO2
X
NHR
Cl
NO2
X
56, R=COCH3
98, R=H
O2N
O
NHR
AcHN
NO2
99, R = H
100, R=COCH3
III (X = O)

Scheme 8

Raney-nickel to give 4,4'-diaminodiphenyl ether (103)[39]. Acetylation of 103 with acetic anhydride gave 4,4'-diacetamidodiphenyl ether (104) which was nitrated using acetic acid-nitric acid mixture to yield 4,4'-diacetamido-3,3'-dinitrodiphenyl ether (105) in good yield. Hydrolysis of 105 by 50% HCl or 10% aqueous KOH gave 4,4'-diamino-3,3'-dinitrodiphenyl ether (106) which was conveniently reduced with freshly washed Raney-nickel and hydrazine-hydrate to afford 3,3',4,4'-tetra-aminodiphenyl ether (107). Treatment of 107 with 1,3-dicarbalkoxy-S-methylisothioureas yielded the title compounds 2,2'-dicarbalkoxyamino-5,5'-dibenzimidazolyl oxides (110 and 111). Further reaction of 86 with 98% formic and glacial acetic acids yielded the corresponding dibenzimidazoles (108 and 109) (Scheme 9).

Reaction of 1,2-ethanedithiol with 56 in presence of KOH did not afford the desired compound 113 which would have yielded 1,2-di-(3-amino-4-nitrophenylthio)ethane (112) on deacetylation. The latter compound was prepared conveniently by treating 98 with 1,2-ethanedithiol which was reduced with 10% Pd/C in large excess of ethanol under high pressure of H_2 in a Paar hydrogenator to give very poor yield of the tetra-amine 114. Treatment of 114 with 1,3-dicarbalkoxy-S-methylisothioureas in refluxing ethanol gave 1,2-di-(2-carbalkoxyaminobenzimidazolyl-5(6)-thio)ethanes (115 and 116) (Scheme 10).



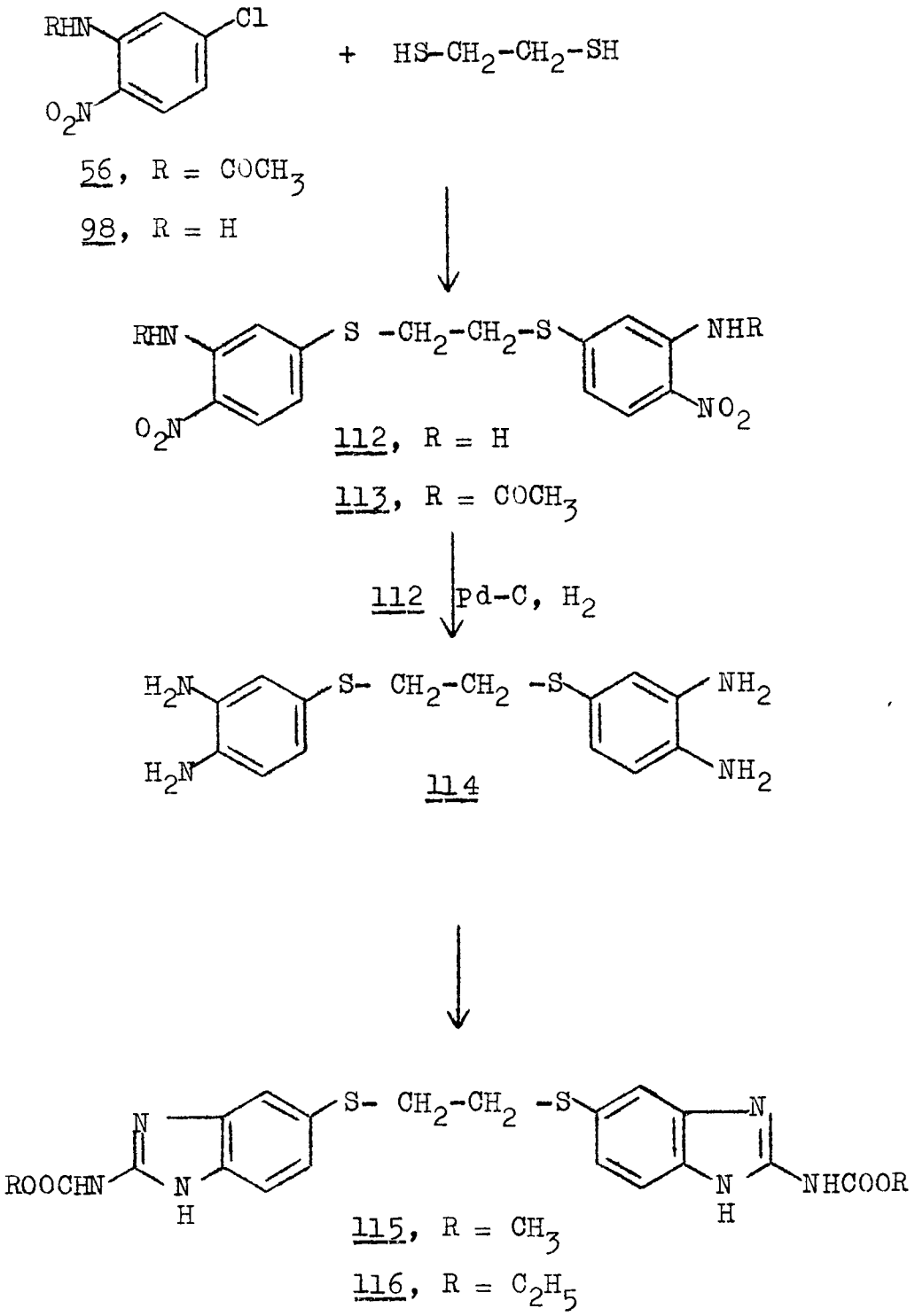
108, R = H

109, R = CH_3

110, R = $NHCOOCH_3$

111, R = $NHCOOC_2H_5$

Scheme - 9

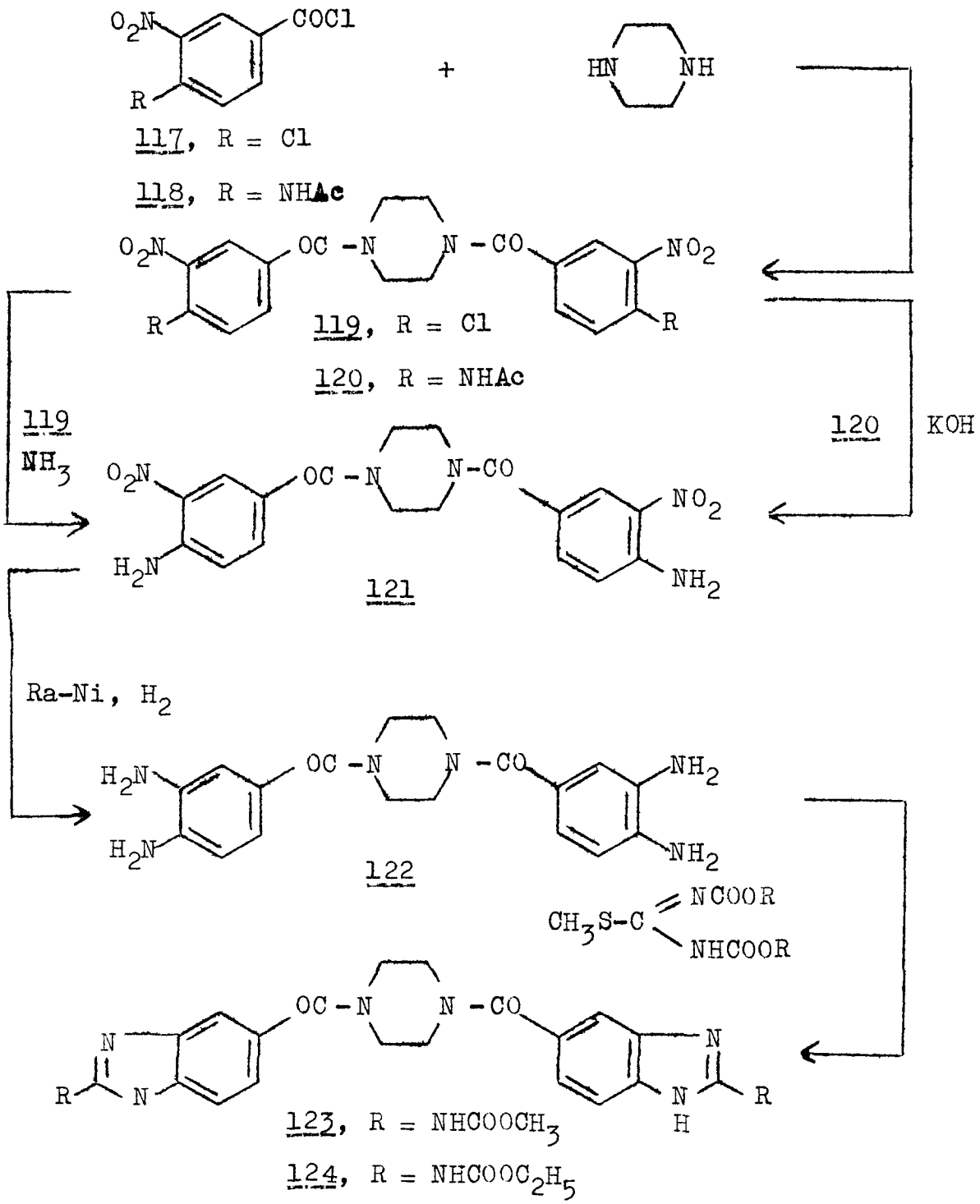

RHN
Cl
O_2N
+ HS-CH_2-CH_2-SH
56, R = $COCH_3$
98, R = H
RHN
S -CH_2-CH_2-S
NHR
O_2N
NO_2
112, R = H
113, R = $COCH_3$
112 Pd-C, H_2
H_2N
S- CH_2-CH_2 -S
NH_2
H_2N
NH_2
114
ROOCHN
N
H
S- CH_2-CH_2 -S
N
N
H
NHCOOR
115, R = CH_3
116, R = C_2H_5

Scheme 10

4-Chloro-3-nitrobenzoyl chloride (117), obtained by treatment of 4-chloro-3-nitrobenzoic acid with $SOCl_2$, was reacted with anhydrous piperazine to get 1,4-di-(4-chloro-3-nitrobenzoyl)piperazine (119). Treatment of 119 with ammonia in DMSO gave very poor yield of the diamine 121 which was prepared in better yields by treating anhydrous piperazine with 4-acetamido-3-nitrobenzoyl chloride (118) in dry benzene to get 1,4-di-(4-acetamido-3-nitrobenzoyl) piperazine (120). The selective hydrolysis of 120 with aqueous KOH in ethanol at room temperature gave 1,4-di-(4-amino-3-nitrobenzoyl)piperazine (121). Reduction of 121 using Raney-nickel and hydrogen in THF or ethanol at 3.5 kg/cm^2 pressure in a Paar hydrogenator afforded 1,4-di-(3,4-diaminobenzoyl)piperazine (122) which reacted with 1,3-dicarbalkoxy-S-methylisothioureas in ethanol to yield the corresponding 1,4-di-(2-carbalkoxyaminobenzimidazolyl-5(6)-carbonyl)piperazines (123 and 124) (Scheme 11).

3.4 Synthesis of 2,5(6)-diarylbenzimidazoles and their cyclic analogs

4-Amino-3-nitrobiphenyl (125)[40], obtained by subsequent nitration, reduction, acetylation, nitration and hydrolysis of biphenyl, was reduced with hydrazine-hydrate and Raney-nickel in ethanol-THF mixture to give 3,4-diaminobiphenyl (126)[41]. Treatment of 126 with 1,3-dicarbethoxy-S-methylisothiourea afforded ethyl 5(6)-phenyl-


117, R = Cl
118, R = NHAc
119, R = Cl
120, R = NHAc
119
NH3
120
KOH
121
Ra-Ni, H2
122
123, R = NHCOOCH3
124, R = NHCOOC2H5

Scheme 11

benzimidazole-2-carbamate (127). When 125 was treated with different benzoyl chlorides in refluxing dry benzene the corresponding 4-(aroyl)amino-3-nitrobiphenyls (128-130) were obtained. Reduction of 128-130 with hydrazine-hydrate and Raney-nickel gave 3-amino-4-(aroyl)aminobiphenyls (131-133) which were subjected to acid catalysed cyclization in ethanol to give the corresponding 2-substituted benzimidazoles (134-136)[42]. Treatment of 136 with thiophosgene in acetone yielded 2-(4-isothiocyanatophenyl)-5(6)-phenylbenzimidazole hydrochloride (139). Similarly, reaction of 136 with ethyl and methyl chloroformates afforded 2-(4-carbalkoxyaminophenyl)-5(6)-phenylbenzimidazoles (140 and 141). Treatment of 135 with alkyl chloroformates or potassium ethyl xanthate yielded the cyclic products 9-phenylbenzimidazo[1,2-c]quinazolin-6-one and 6-thione (137 and 138). When 135 was allowed to react with methyl and ethyl chloroformate in acetone it yielded a mixture of 137 and 114. The structure of 137 and 138 was confirmed by their mass and ^{13}C-NMR spectra. 137 and 138 had their M^+ at m/z 311 and 327 which corresponds to the cyclic products. The ^{13}C-NMR spectrum of 137 in DMSO-d_6 showed the chemical shift of C-9 at 135.31 δ which was in agreement with the calculated value (136.1 δ) if structure 137 is taken into account. Had the cyclization occurred through the other nitrogen to yield its positional isomer 10-phenylbenzimidazo

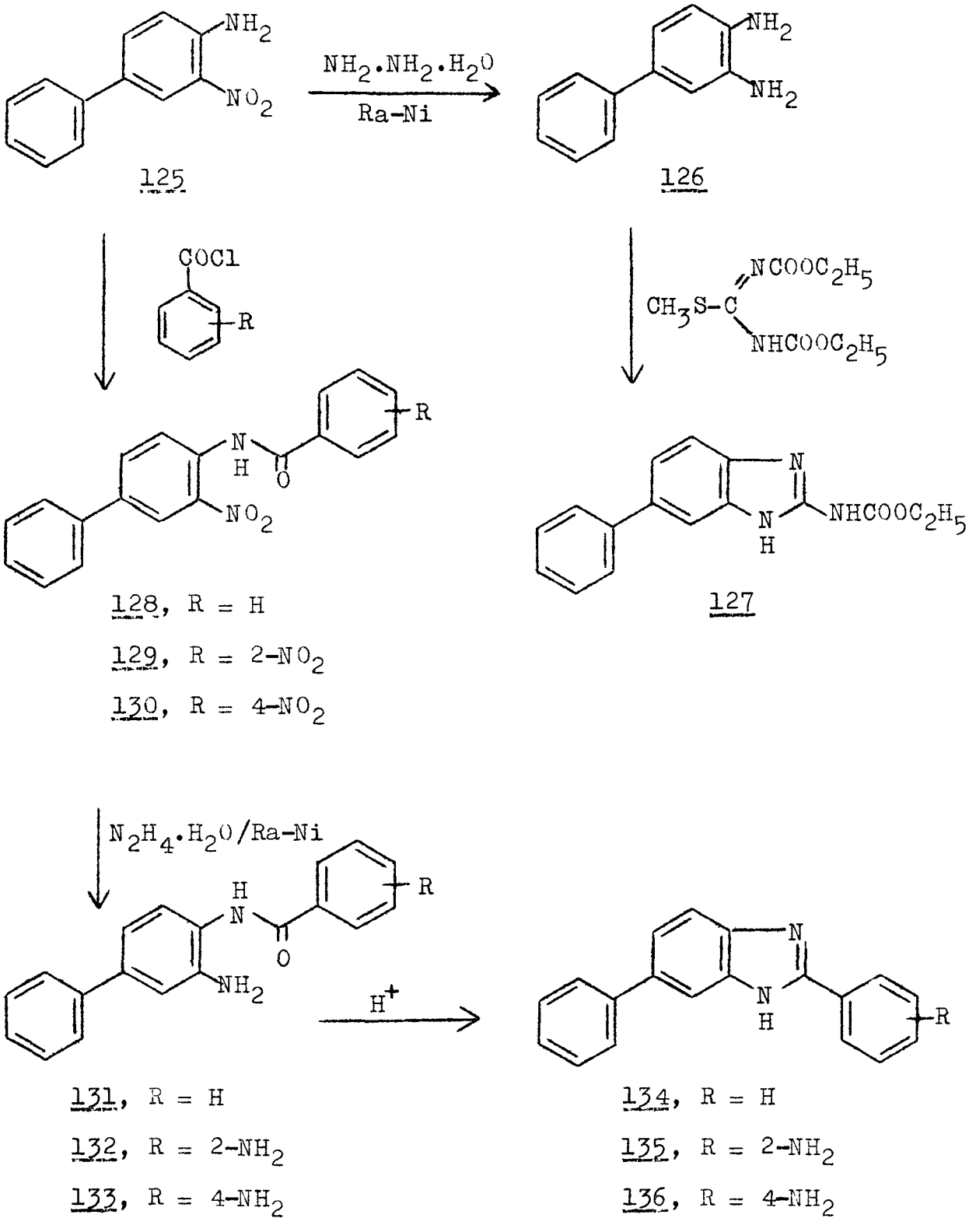
[1,2-c]quinazolin-6-one, the calculated value for C-10 would have been at δ 130.0. The calculation is based on the effect of various groups present in 5-phenylbenzimidazole fused with a quinazolin-nucleus[43,44]. The structure of 137 was further supported by the fact that ^{13}C-NMR of 5(6)-phenylbenzimidazole and 2-(2-aminophenyl)-5(6)-phenylbenzimidazole (135) showed the absorption for 5(6)-carbon at δ 133.14 and 132.98 respectively.

Treatment of 133 with two moles of thiophosgene in presence of triethylamine yielded 1-(4-isothiocyanatobenzoyl)-2-mercapto-5-phenylbenzimidazole (145). When 132 was allowed to react with two moles of thiophosgene under similar experimental conditions, it yielded only 144 out of three possible products 142, 144 and 146. The structure was supported by its IR and mass spectra. The IR spectra of 144 and 145 had sharp bands at 1640 and 1635 cm^{-1} corresponding to C=N absorption of the benzimidazole ring. The high carbonyl absorption at 1680 and 1710 cm^{-1} in 144 and 145 also supported the formation of these compounds[45] thus excluding the possibility of the presence of 146 in the isolated product. The mass spectra of both the compounds had M^+ at m/z 387 and clearly indicated the loss of a thiol group (32) from the (M^+-161) at m/z 194 in 144 and from molecular ion at m/z 355 in 145 which is not possible in uncyclized products.

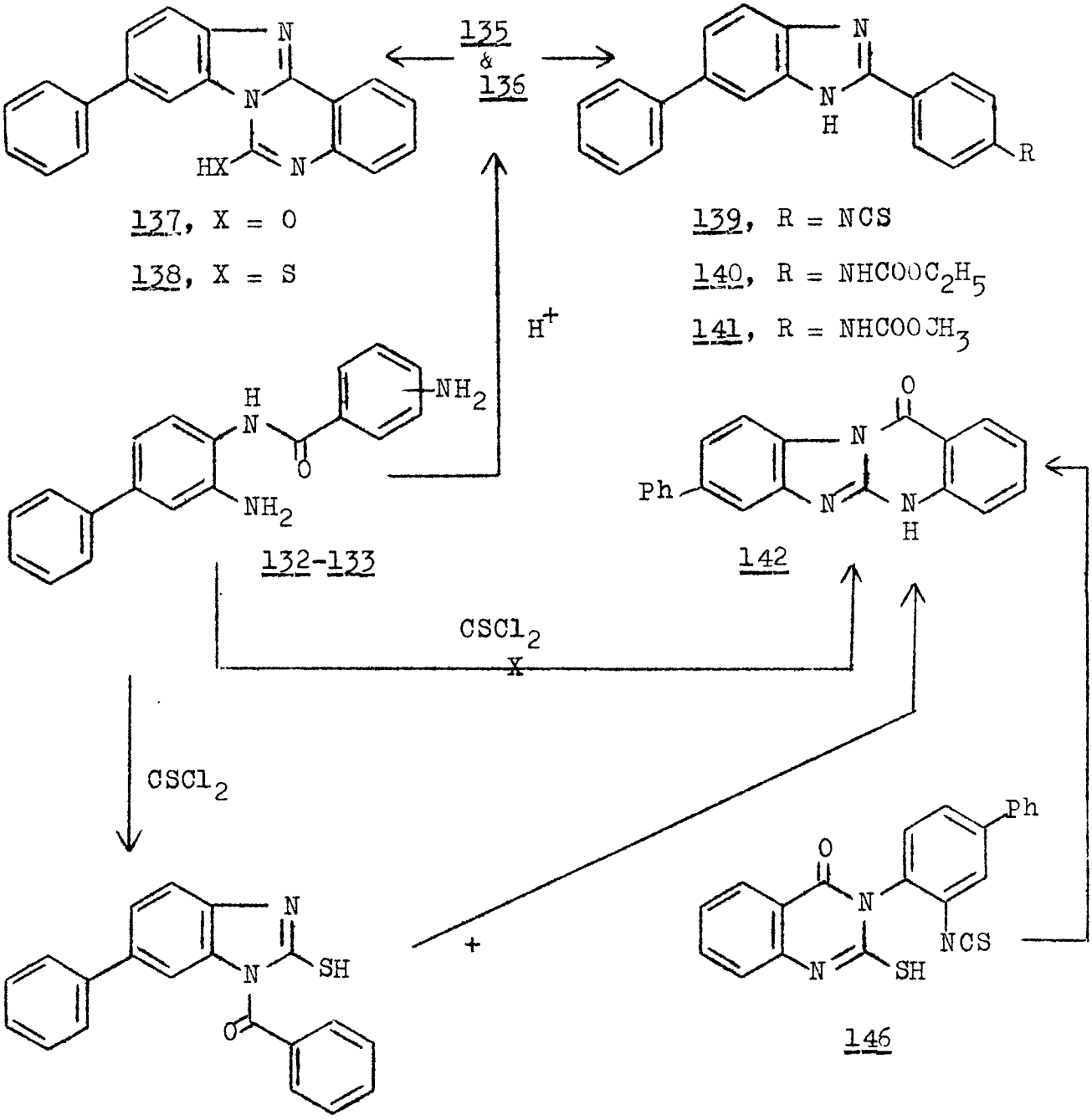
The reaction of 132 with one mole of thiophosgene resulted in the formation of only 1-(2-aminobenzoyl)-2-mercapto-5-phenylbenzimidazole (143) along with the small amount of corresponding isothiocyanate 144. The structure of 143 was confirmed by its mass (M^+ at m/z 345), and IR absorption (1690 cm^{-1} for NCON-C_6H_4-2-NH_2)[45]. Furthermore, isolation of 144 from the reaction mixture can only be accounted by formation of 143 as intermediate (Scheme 12).

3.5 Synthesis of 2-substituted 5(6)-(4-substitutedphenoxy, phenylthio and sulfono)benzimidazoles

Reaction of 4-acetamidothiophenol with 5-chloro-2-nitroacetanilide (56) and 5-chloro-2-nitroaniline (98) in presence of KOH in n-propanol gave excellent yields of 5-(4-acetamidophenylthio)-2-nitroaniline (147) and 5-(4-acetamidophenylthio)-2-nitroacetanilide (148) respectively. Alternatively, 147 was also prepared by selective hydrolysis of 148 with aqueous KOH. Reduction of 147 with hydrazine-hydrate and Raney-nickel in THF-ethanol mixture afforded 4-(4-acetamidophenylthio)-o-phenylenediamine (149) which was condensed with 1,3-dicarbalkoxy-S-methylisothioureas in refluxing ethanol to afford alkyl 5(6)-(4-acetamidophenylthio)benzimidazole-2-carbamates (150 and 151) in good yields. 149 was also treated with formic and glacial acetic acids to give the corresponding benzimidazole (152) and 2-methylbenzimidazole (153). Selective hydrolysis of amido function



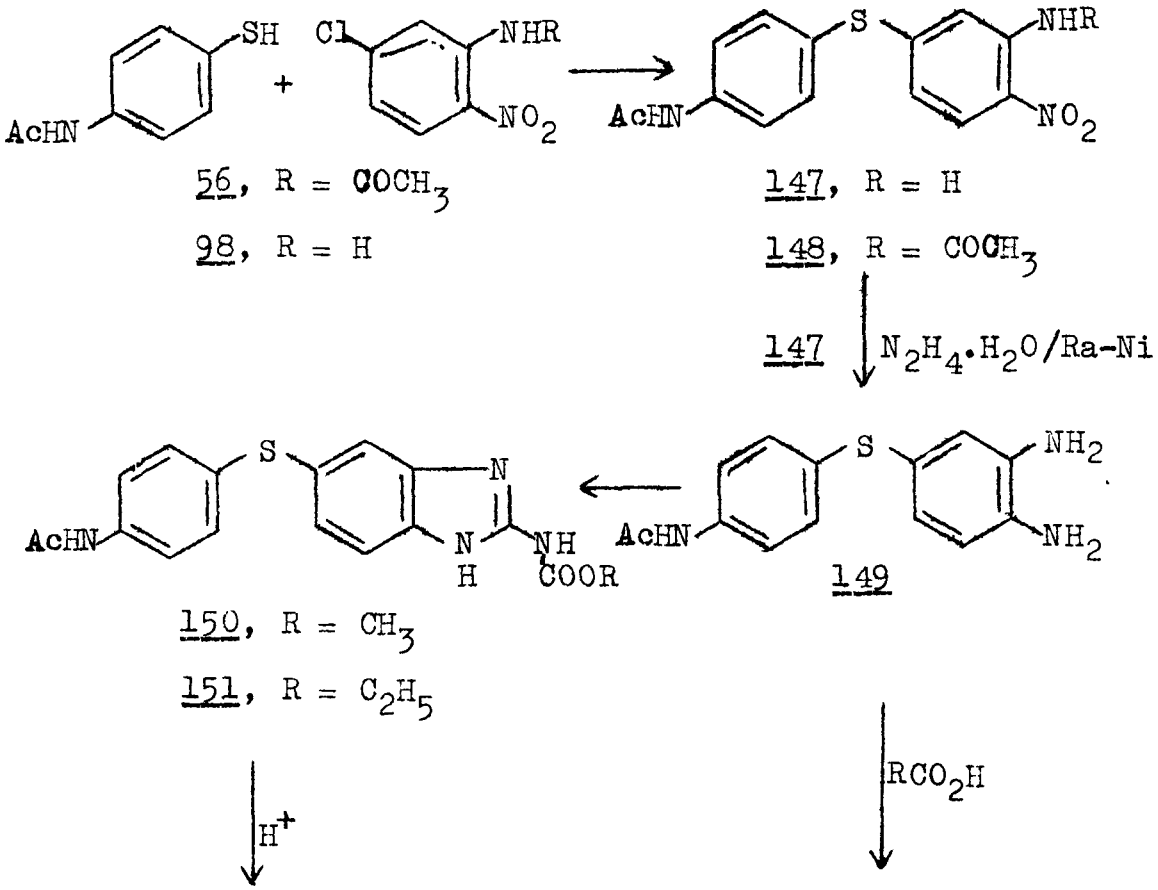
Scheme 12 (Contd.)


135
&
136
137, X = O
138, X = S
139, R = NCS
140, R = NHCOOC2H5
141, R = NHCOOCH3
H+
132-133
142
CSCl2
X
CSCl2
146
143, R = 2-NH2
144, R = 2-NCS
145, R = 4-NCS

Scheme 12

in 150 and 151 with 10% HCl afforded the alkyl 5(6)-(4-aminophenylthio)benzimidazole-2-carbamates (154 and 155)[46]. A similar hydrolysis of 152 and 153 using concentrated HCl yielded the corresponding amines (156 and 157). However, when 150 and 151 were refluxed in 50% HCl for a longer period, complete hydrolysis of the compounds took place giving rise to 2-amino-5(6)-(4-aminophenylthio)benzimidazole (158).

Oxidation of 150-153 was carried out using 80% aqueous acetic acid and $KMnO_4$ at room temperature to yield their corresponding sulfones (159-162) of which 159 and 160 were selectively hydrolysed with 10% HCl to yield alkyl 5(6)-(4-aminophenylsulfono)benzimidazole-2-carbamates (163 and 164). Similarly, 161 and 162 were hydrolysed with 50% HCl to give 5(6)-(4-aminophenylsulfono)benzimidazole (166) and 2-methyl-5(6)-(4-aminophenylsulfono)benzimidazole (167) while hydrolysis of 159 or 160 in 50% HCl yielded 2-amino-5(6)-(4-aminophenylsulfono)benzimidazole (165). The amines 154, 155, 163 and 164 were allowed to react with thiophosgene in presence of triethylamine in large volume of acetone (due to their poor solubility in acetone) to afford their corresponding isothiocyanates 168, 169, 172 and 173 respectively. Treatment of thiophosgene with 157, 158, 166 and 167 in acetone and triethylamine also yielded the desired isothiocyanates 170, 171, 174 and 175 (Scheme 13).



56, R = $COCH_3$

98, R = H

147, R = H

148, R = $COCH_3$

147 $N_2H_4.H_2O$/Ra-Ni

149

150, R = CH_3

151, R = C_2H_5

H^+

RCO_2H

152, R = H

153, R = CH_3

154, R = $NHCOOCH_3$

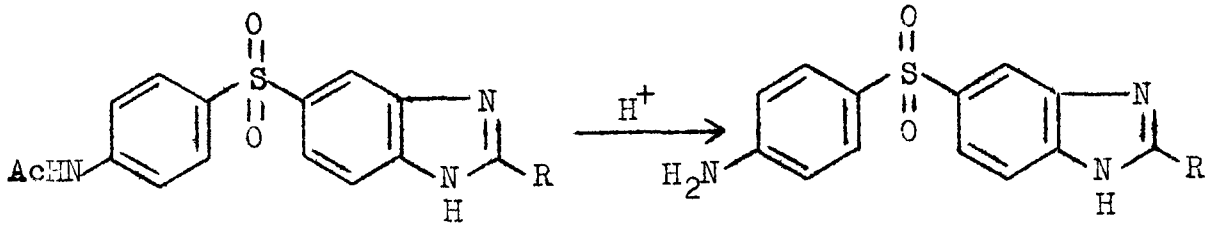
155, R = $NHCOOC_2H_5$

156, R = H

157, R = CH_3

158, R = NH_2

Scheme 13 (Contd.)



159, R = $NHCOOCH_3$

160, R = $NHCOOC_2H_5$

161, R = H

162, R = CH_3

163, R = $NHCOOCH_3$

164, R = $NHCOOC_2H_5$

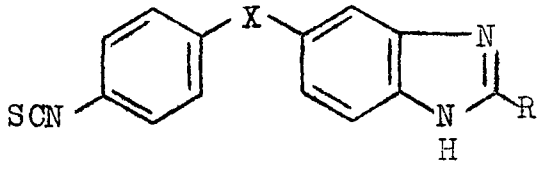
165, R = NH_2

166, R = H

167, R = CH_3

150-153 $\xrightarrow{KMnO_4}$ 150-157

150-157 $\xrightarrow[154\text{-}157]{CSCl_2}$



168, R = $NHCOOCH_3$, X = S

169, R = $NHCOOC_2H_5$, X = S

170, R = H, X = S

171, R = CH_3, X = S

172, R = $NHCOOCH_3$, X = SO_2

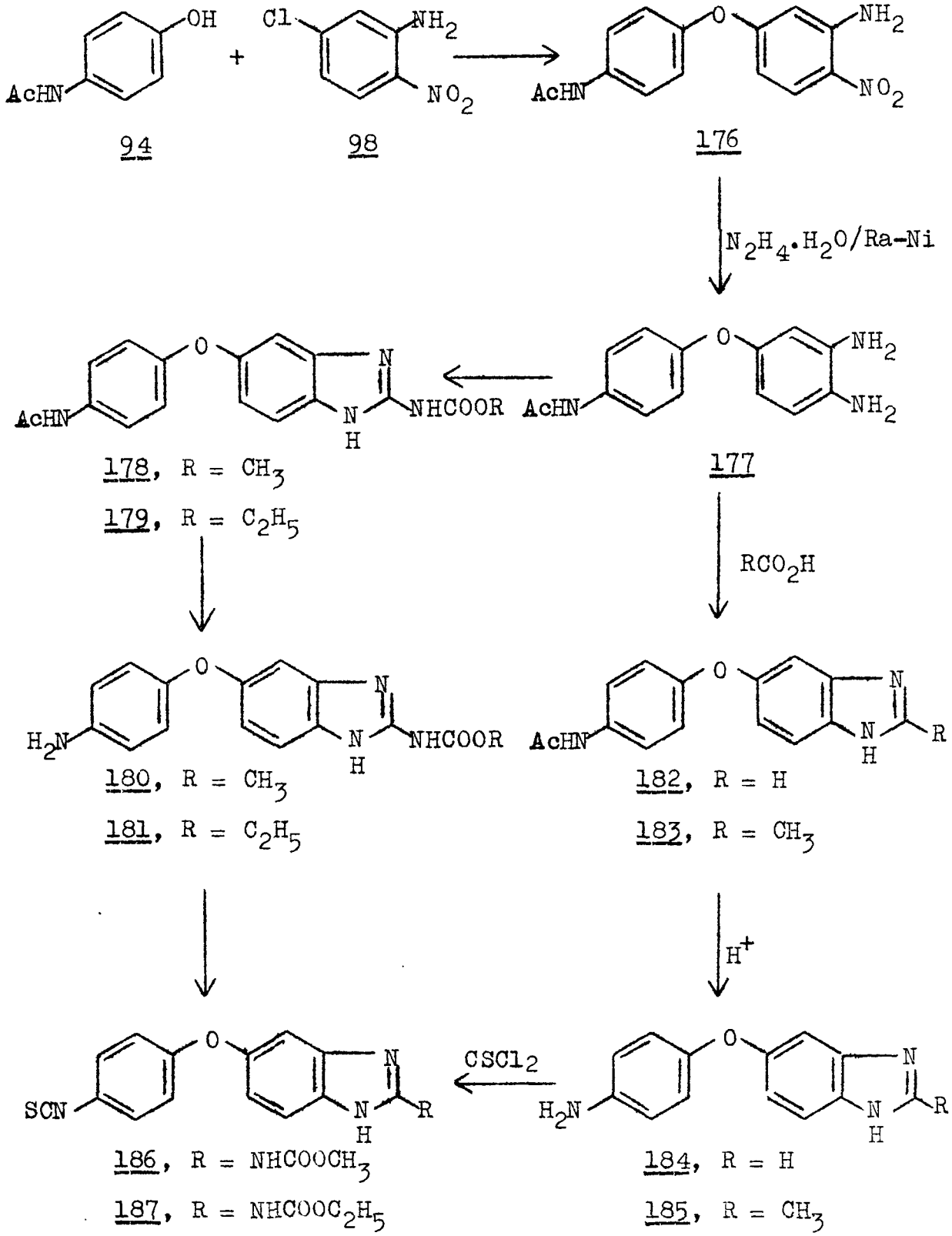
173, R = $NHCOOC_2H_5$, X = SO_2

174, R = H, X = SO_2

175, R = CH_3, X = SO_2

Scheme 13

Reaction of 4-acetamidophenol (94) and 5-chloro-2-nitroaniline (98) in presence of KOH in dry DMF yielded 5-(4-acetamidophenoxy)-2-nitroaniline (176) in 44% yield. 176 was reduced with hydrazine-hydrate and Raney-nickel in THF-ethanol mixture to give 4-(4-acetamidophenoxy)-o-phenylenediamine (177) which was not isolated and was used as such in further reactions. Reaction of 177 with 1,3-dicarbalkoxy-S-methylisothioureas in refluxing ethanol gave alkyl 5(6)-(4-acetamidophenoxy)benzimidazole-2-carbamates (178 and 179) which were hydrolysed selectively with 10% HCl to give the corresponding amines (180 and 181). Reaction of 177 with formic and glacial acetic acids yielded 5(6)-(4-acetamidophenoxy)benzimidazole (182) and 2-methyl-5(6)-(4-acetamidophenoxy)benzimidazole (183) respectively which were isolated as their hydrochlorides. Hydrolysis of 182 and 183 in concentrated HCl afforded the corresponding amines 184 and 185 as their hydrochlorides which were basified with aqueous ammonia to give the free bases. The amines 180, 181, 184, 185 were treated with thiophosgene in acetone in presence of two moles of triethylamine to give their corresponding 5(6)-(4-isothiocyanatophenoxy)benzimidazoles (186-189) (Scheme 14).



94, 98, 176, 177, 178, R = CH_3, 179, R = C_2H_5, 180, R = CH_3, 181, R = C_2H_5, 182, R = H, 183, R = CH_3, 184, R = H, 185, R = CH_3, 186, R = $NHCOOCH_3$, 187, R = $NHCOOC_2H_5$, 188, R = H, 189, R = CH_3

Scheme 14

3.6 Synthesis of 5(6)-thiophenoxy and phenoxymethyl benzimidazole-2-carbamates

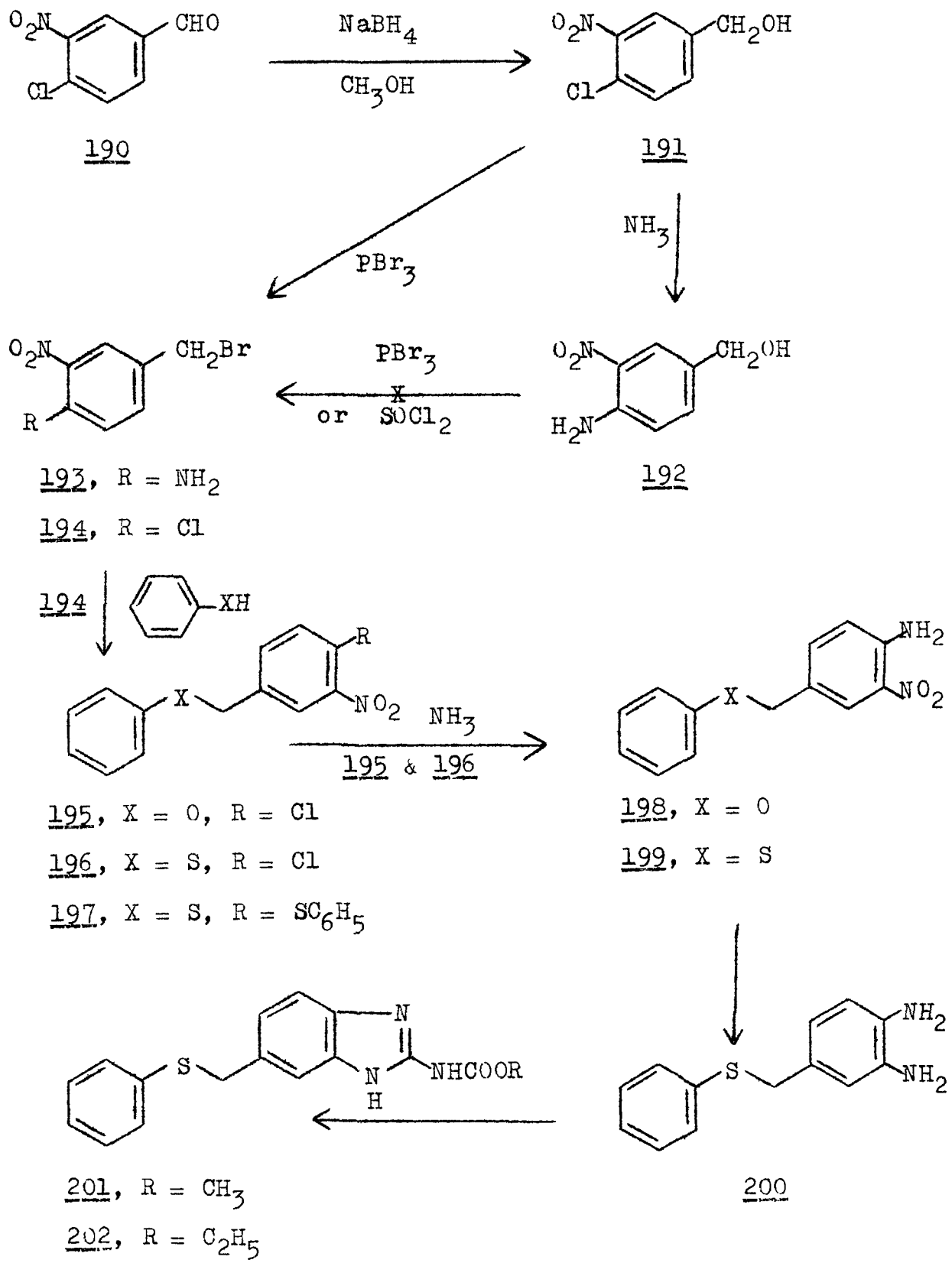
4-Chloro-3-nitrobenzaldehyde (190)[47], prepared by nitration of 4-chlorobenzaldehyde in KNO_3-H_2SO_4, was reduced with sodium borohydride in methanol to give 4-chloro-3-nitrobenzyl alcohol (191)[48] . Treatment of 191 with ammonia in steel bomb at 150°C gave the corresponding amino compound 192 which could not be converted to its bromide or chloride by action of PBr_3 or thionyl chloride. However, when 191 was treated with PBr_3 in dry benzene it gave 4-chloro-3-nitrobenzyl bromide (194) in good yield which was treated with phenol and thiophenol in presence of K_2CO_3 in acetone to give 2-nitro-4-(phenoxy) and 2-nitro -4-(thiophenoxy)methylchlorobenzenes (195 and 196). When 194 was allowed to react with one mole of thiophenol in ethanol in presence of KOH it yielded a mixture of 196 and 2-thiophenoxy-5-thiophenoxymethylnitrobenzene (197) in poor yields. However, better yield of 197 was obtained when two moles of thiophenol was reacted with one mole of 194 in ethanolic potassium hydroxide. Reaction of 195 with aqueous ammonia solution in THF at 150°C in a steel bomb gave 2-nitro-4-phenoxymethylaniline (198). Similarly 196 was treated with aqueous ammonia in THF at 150°C in steel bomb to yield the amine 199 which could not be isolated. However, 199 was obtained when ethanol was

taken as solvent in place of THF in the above reaction. Attempts to reduce 198 with hydrazine-hydrate and Raney-nickel, Raney-nickel and H_2 or $FeSO_4$-NH_3 were unsuccessful as it always gave a complex mixture of the products. In contrary, 199 was reduced smoothly with $FeSO_4$-NH_3 in acetone to give the required diamine 200 in good yield which was treated with 1,3-dicarbalkoxy-S-methylisothioureas in refluxing ethanol to afford alkyl 5(6)-thiophenoxymethylbenzimidazole-2-carbamates (201 and 202)* (Scheme 15).

3.7 Synthesis of 1,2-disubstituted ethanes and 1,3-disubstituted propanes

Reaction of 4-acetamidothiophenol with 1,2-dibromoethane and 1,3-dibromopropane in presence of KOH yielded 1,2-di-(4-acetamidophenylthio)ethane (203) and 1,3-di-(4-acetamidophenylthio)propane (204) which were oxidized with $KMnO_4$ in 80% aqueous acetic acid to give the corresponding sulfones (205 and 206). Hydrolysis of 203, 205 and 206 with concentrated HCl gave respective 1,2-di-(4-aminophenylthio) and 1,2-di-(4-aminophenylsulfono)ethanes (207 and 208) and 1,3-di-(4-aminophenylsulfono)propane (209) respectively. Treatment of 207-209 with thiophosgene in 50% aqueous acetic acid or 10% HCl

*During the course of our investigation Haugwitz et al.[49] reported the synthesis and biological activity of compound 201 with no data.



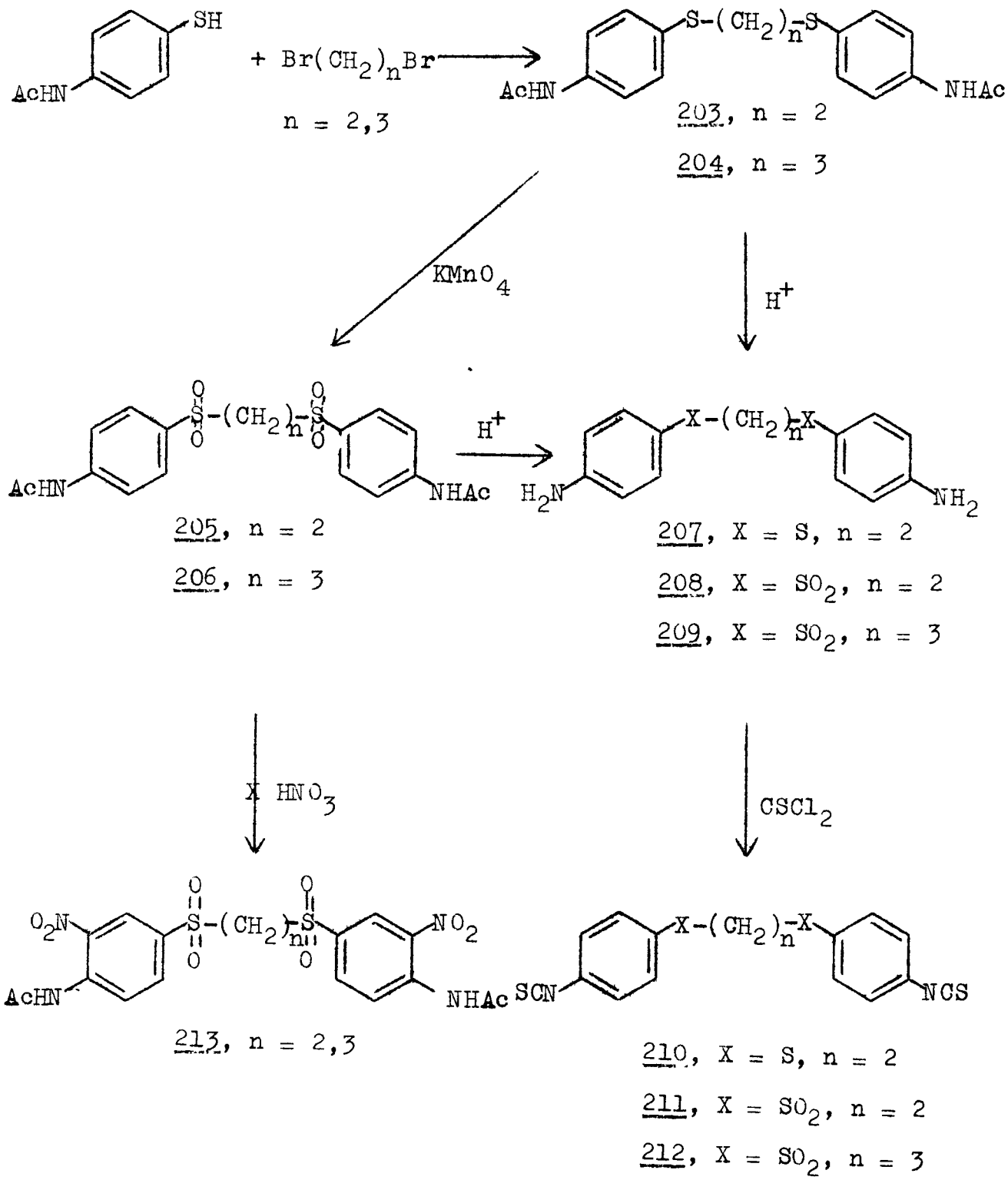
190 191 192 193, R = NH_2 194, R = Cl 195, X = O, R = Cl 196, X = S, R = Cl 197, X = S, R = SC_6H_5 198, X = O 199, X = S 200 201, R = CH_3 202, R = C_2H_5

Scheme 15

afforded the corresponding 1,2-di-(4-isothiocyanato-phenylthio) and 1,2-di-(4-isothiocyanatophenylsulfono) ethanes (210 and 211) and 1,3-di-(4-isothiocyanatophenyl-sulfono)propane (212). Nitration of 205 and 206 under different experimental conditions failed to yield the required dinitro compound 213 and hence, dibenzimidazoles of the type III ($X=SO_2-(CH_2)_n-SO_2$, $n = 2,3$) could not be prepared (Scheme 16).

3.8 Synthesis of substituted thiocarboxamides, carboxamides and thioureas

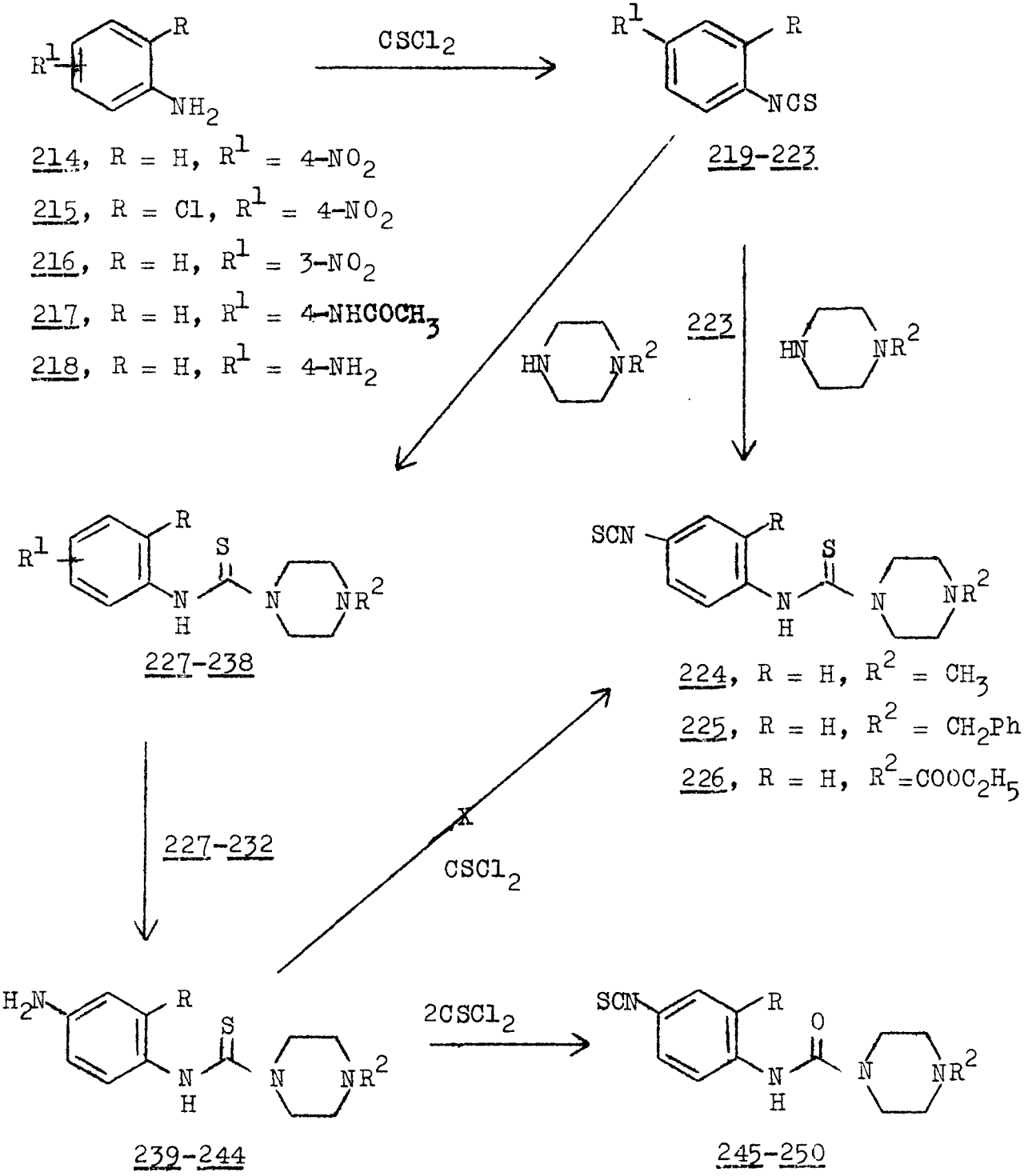
Substituted phenylisothiocyanates (219-223) were prepared by treatment of the corresponding anilines (214-218) with thiophosgene in acetone or 10% HCl. Reaction of 4-substituted piperazines with 219-222 yielded the corresponding substituted phenyl-4-substituted-1-piperazinylthiocarboxamides (227-238) in good yields. Attempts to reduce 227-238 by Raney-nickel and H_2, hydrazine-hydrate and Raney-nickel, sodium dithionite Zn-CH_3COOH or Sn-HCl were unsuccessful. However, 227-238 were successfully reduced with $FeSO_4$-NH_3 using large volume of aqueous ammonia (as they are poorly soluble even in hot aqueous ammonia). The reactions of amines (239-244), obtained by $FeSO_4$-NH_3 reduction, with one mole of thiophosgene in acetone led to an unusual desulphurization of thiocarboxamides to their corresponding


SH
AcHN
+ Br(CH2)nBr
n = 2,3
S-(CH2)n-S
AcHN
NHAc
203, n = 2
204, n = 3
KMnO4
H+
O
S-(CH2)n-S
O
AcHN
NHAc
H+
X-(CH2)n-X
H2N
NH2
205, n = 2
206, n = 3
207, X = S, n = 2
208, X = SO2, n = 2
209, X = SO2, n = 3
X HNO3
CSCl2
O2N
NO2
AcHN
NHAc
SCN
NCS
213, n = 2,3
210, X = S, n = 2
211, X = SO2, n = 2
212, X = SO2, n = 3

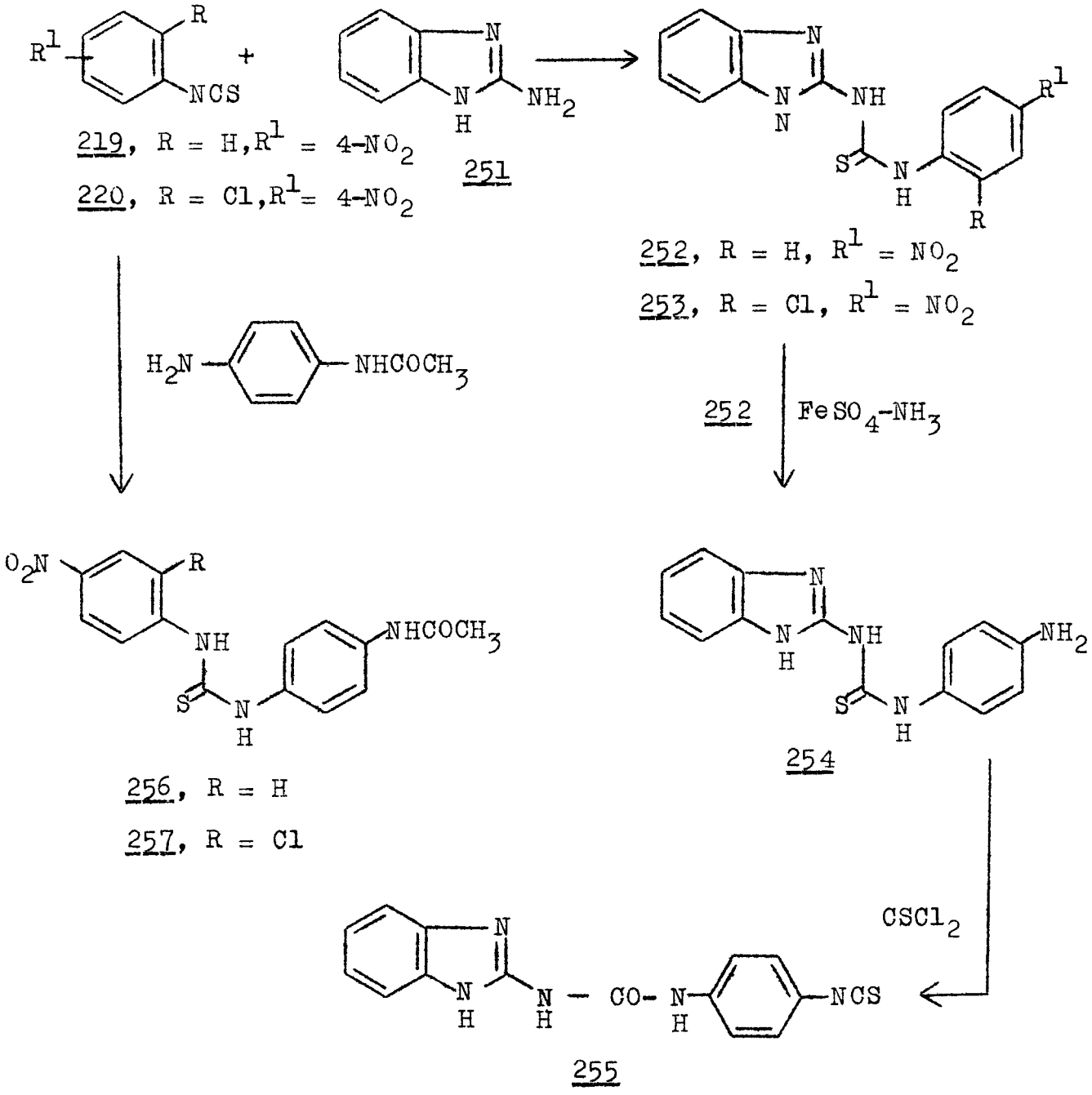
Scheme 16

carboxamides along with formation of isothiocyanates which were isolated in poor yields. A similar reaction of 239-244 with two moles of thiophosgene yielded the 4-isothiocyanatophenyl-4-substituted-1-piperazinylcarboxamides (245-250) in good yield and no corresponding thio analogs could be isolated. The 4-isothiocyanatophenyl-4-substituted-1-piperazinylthiocarboxamides (224-226) were prepared by reaction of one mole of 4-substituted piperazines on 1,4-phenylenediisothiocyanate (223) in acetone under high dilution at room temperature and the product purified by crystallization or by column chromatography (Scheme 17).

Reaction of 2-aminobenzimidazole (251) with 4-nitrophenylisothiocyanate (219) and 2-chloro-4-nitrophenylisothiocyanate (220) in refluxing ethyl acetate gave N-(4-nitrophenyl)-N'-(2-benzimidazolyl)thiourea (252) and N-(2-chloro-4-nitrophenyl)-N'-(2-benzimidazolyl) thiourea (253). The $FeSO_4$-NH_3 reduction of 252 gave the required N-(4-aminophenyl)-N'-(2-benzimidazolyl)thiourea (254) which was treated with two moles of thiophosgene to yield N-(4-isothiocyanatophenyl)-N'-(2-benzimidazolyl)urea (255). Similar reaction of 4-aminoacetanilide with 219 and 220 gave the N-(4-acetamidophenyl)-N'-(4-nitrophenyl)thiourea (256) and N-(4-acetamidophenyl)-N'-(2-chloro-4-nitrophenyl)thiourea (257) respectively (Scheme 18).


CSCl2
214, R = H, R1 = 4-NO2
215, R = Cl, R1 = 4-NO2
216, R = H, R1 = 3-NO2
217, R = H, R1 = 4-NHCOCH3
218, R = H, R1 = 4-NH2
219-223
223
227-238
224, R = H, R2 = CH3
225, R = H, R2 = CH2Ph
226, R = H, R2=COOC2H5
227-232
CSCl2
2CSCl2
239-244
245-250

Scheme 17


219, R = H, R1 = 4-NO2
220, R = Cl, R1 = 4-NO2
251
252, R = H, R1 = NO2
253, R = Cl, R1 = NO2
252
FeSO4-NH3
256, R = H
257, R = Cl
254
CSCl2
255

Scheme 18

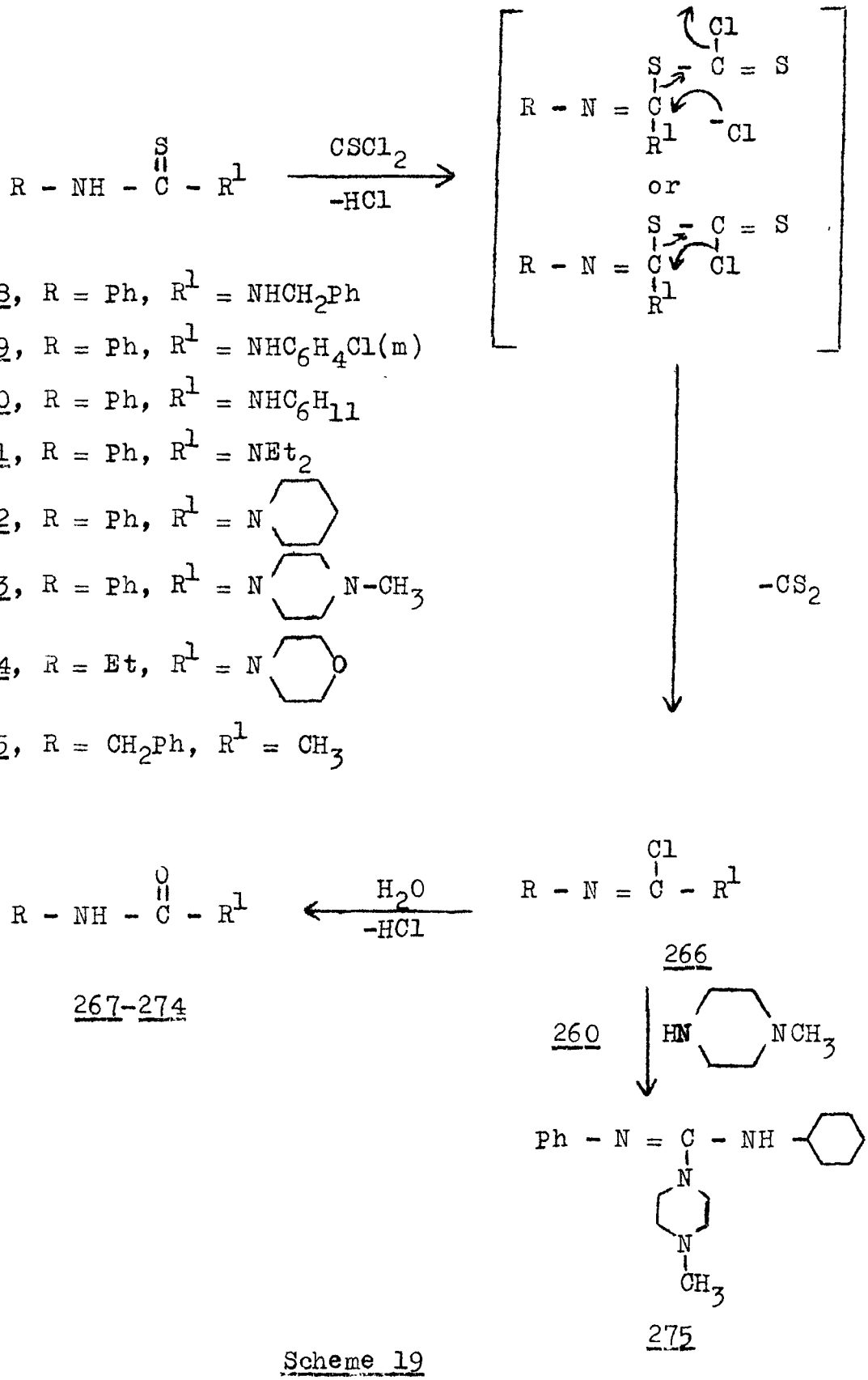
Keeping in view the ability of thiophosgene to desulphurize thioureas and thiocarboxamides, the reaction was extended to thioamide also, and its conversion to corresponding amide was demonstrated. Thus, a number of thioureas, thiocarboxamides (258-264) and thioamide (265), when reacted with thiophosgene in acetone at room temperature gave the corresponding ureas and carboxamides (267-273) and amide (274). The thioureas and the thiocarboxamides (258-264) were prepared by reaction of phenyl and alkyl isothiocyanates with corresponding amines. The products obtained after thiophosgene treatment were compared (mixed m.p., Co-IR and Co-TLC) with the ureas and carboxamides prepared directly from phenyl or alkyl isocyanates with amines and acetamide obtained by reaction of acetic anhydride with benzylamine (267-274).

A probable mechanism of desulphurization involves the initial attack of sulphur of thioureas, thiocarboxamides or thioamide (258-265) at thiophosgene resulting in the formation of an activated complex which on synchronous loss of carbondisulfide affords the chloro intermediate (266). Alternatively, 266 may also be obtained by nucleophilic reaction of the chloride ion on the activated complex. Simultaneous reaction of water with 266 yields the corresponding oxygen analogs (267-274). The intermediacy of 266 was further supported by converting it

into corresponding substituted amidine (275) by action of N-methylpiperazine in dry acetone (Scheme 19).

3.9 Synthesis of 1,4-disubstituted piperazines

Reaction of anhydrous piperazine with 1-chloro-4-nitrobenzene in presence of K_2CO_3 in acetone in steel bomb at 150°C gave 1-(4-nitrophenyl)piperazine (276) and no 1,4-di-(4-nitrophenyl)piperazine (277) could be isolated. When 276 was allowed to react with 4-nitrobenzoyl chloride in dry benzene in presence of triethylamine, it yielded 1-(4-nitrobenzoyl)-4-(4-nitrophenyl)piperazine (278) which was reduced with $FeSO_4$-NH_3 to give the corresponding diamine (279). Treatment of 279 with thiophosgene in acetone in presence of triethylamine gave 1-(4-isothiocyanatobenzoyl)-4-(4-isothiocyanatophenyl)piperazine (280). Similarly, anhydrous piperazine reacted with two moles of 4-nitrobenzoyl chloride to yield 1,4-di-(4-nitrobenzoyl) piperazine (281). Reduction of 281 with Raney-nickel and H_2 in a Paar hydrogenator afforded 1,4-di-(4-aminobenzoyl) piperazine (282). The synthesis of 1,4-di-(4-isothiocyanatobenzoyl)piperazine (283) was achieved by reaction of 282 with thiophosgene in 10% HCl-$CHCl_3$ mixture (Scheme 20).



258, R = Ph, R^1 = $NHCH_2Ph$

259, R = Ph, R^1 = $NHC_6H_4Cl(m)$

260, R = Ph, R^1 = NHC_6H_{11}

261, R = Ph, R^1 = NEt_2

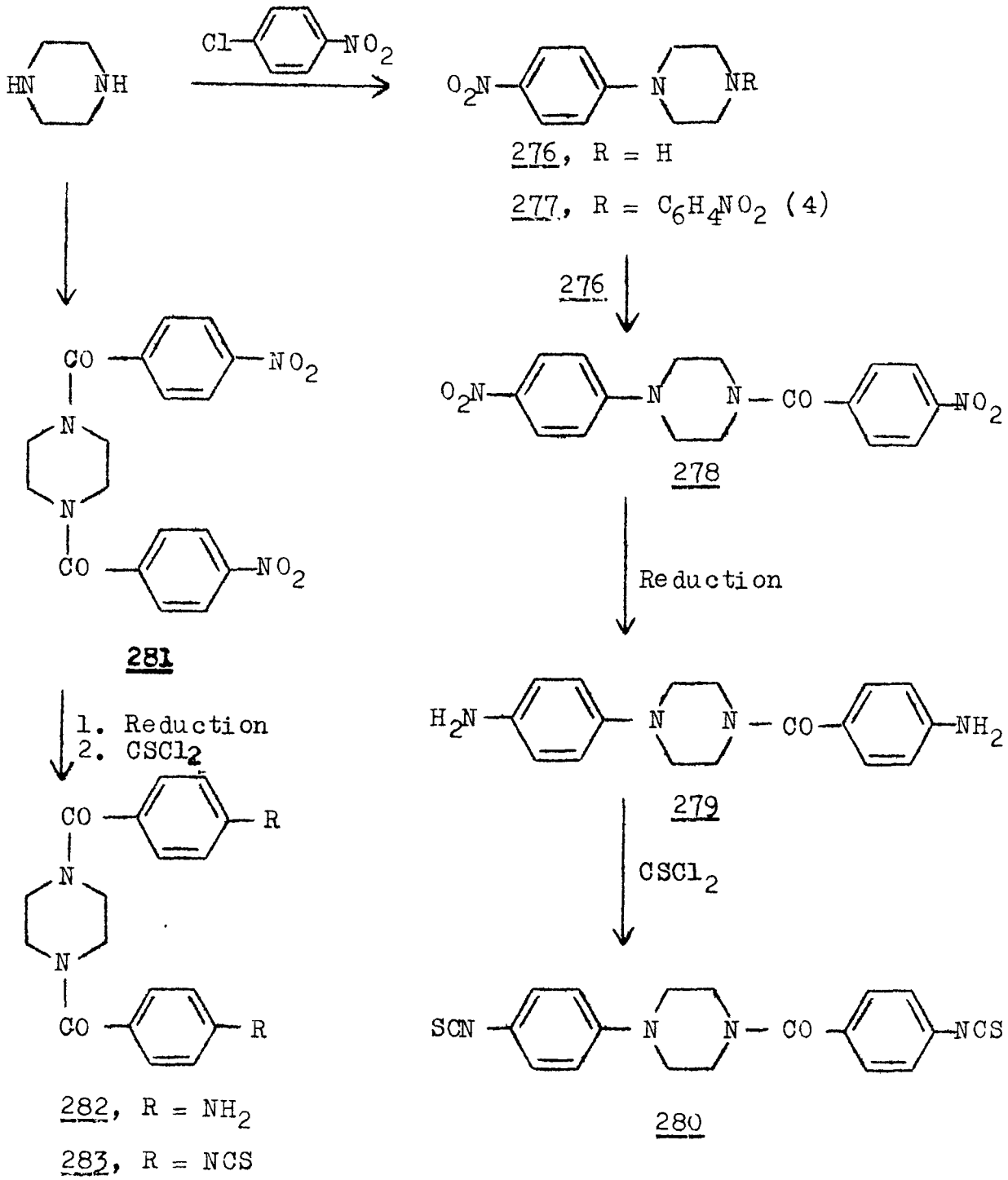
262, R = Ph, R^1 = N

263, R = Ph, R^1 = N N-CH_3

264, R = Et, R^1 = N O

265, R = CH_2Ph, R^1 = CH_3

Scheme 19


Cl
NO2
HN
NH
O2N
N
NR
276, R = H
277, R = C6H4NO2 (4)
276
CO
NO2
N
N
CO
NO2
278
Reduction
281
1. Reduction
2. CSCl2
H2N
N
N
CO
NH2
279
CSCl2
CO
R
N
N
CO
R
SCN
N
N
CO
NCS
282, R = NH2
283, R = NCS
280

Scheme 20

4. EXPERIMENTAL:

The structures of all the compounds were routinely checked by IR recorded on Perkin-Elmer 157 and 177 infracord spectrophotometers. The NMR spectra were obtained on Varian A60-D and EM-360L (60 MHz) or R-32 (90 MHz) spectrometers using TMS as internal reference. Mass spectra were taken on Jeol JMS-D300 (~70 ev) instrument. The purity of all the compounds was checked on silica - gel G-plates and spots were located by I_2 vapours, $KMnO_4$ (2%) spray or Dragendorff's reagent spray. Melting points were taken in sulphuric acid bath and are uncorrected.

Benzimidazole (22) and 2-methylbenzimidazole (23)

These compounds were prepared by treating o-phenylene diamine (13.5 g, 0.125 mol) with formic acid and glacial acetic acid respectively.

22, yield 12 g (81.6%), m.p.171° (lit.[23] m.p.171-2°)
23, yield 9.9 g (60%), m.p.176° (lit.[23] m.p.176°)

2-Methyl-5(6)-nitrobenzimidazole (25)

Conc. nitric acid (13.3 ml, d=1.4) was added dropwise to ice-cooled mixture of 23 (11 g, 0.83 mol) in H_2SO_4 (10 ml, d=1.84) during 30 minutes. The reaction mixture was poured on crushed ice and product isolated, yield

12.5 g (85%), m.p.217° (lit.[24] m.p.219°).

Similarly 5(6)-nitrobenzimidazole (24) was prepared by nitration of 22 in 90% yield, m.p.201-2° (lit.[24] m.p. 203°).

5(6)-Aminobenzimidazole (26)

A mixture of 24 (10 g, 0.061 mol) and Raney-nickel (about 1.5 g) in ethanol (200 ml) was shaken with hydrogen at 3.5 kg/cm^2 in a Paar hydrogenator for 12 hr. The catalyst was filtered out, solvent removed from filtrate and the product was purified as its hydrochloride, yield 4.9 g (60%), m.p.288° (lit.[25] m.p.290°).

Using the above method 27 was obtained as its hydrochloride by reduction of 25, yield 62%, m.p.298° (lit.[25] m.p.298-9°).

5(6)-(2,4-Dinitrophenyl)aminobenzimidazole (28)

A mixture of 26 (4 g, 0.03 mol), 1-chloro-2,4-dinitrobenzene (6.1 g, 0.03 mol) and triethylamine (4.4 ml, 0.03 mol) in 95% ethanol (50 ml) was refluxed for 14 hr. The reaction mixture was cooled and the separated solid filtered, washed successively with cold ethanol (3x10 ml), water (15 ml) and dried, yield 6.27 g (70%), m.p.141°.

IR(KBr) cm^{-1} : 1330, 1580 (NO_2), 1610 (Arom).

NMR(DMSO-d_6)δ : 6.88-7.6 (m, 4H, Ar-H), 8.05 (dd, 1H, Ar-H, p to NO_2, J=2 & 9Hz), 8.1 (s, 1H,

N=CH-N), 8.75 (d, 1H, Ar-H, o to both NO_2, J=3Hz).

Analysis for : $C_{13}H_9N_5O_4$ (299)

Calcd. : C, 52.17; H, 3.01; N, 23.40

Found : C, 52.50; H, 3.35; N, 23.61%.

Similarly 29 was prepared by reaction of 27 with 1-chloro-2,4-dinitrobenzene in ethanol, yield 70%, n.p. $>300^{\circ}$.

IR(KBr) cm^{-1} : 1325, 1580 (NO_2), 1615 (Arom).

NMR($CDCl_3$ + DMSO-d_6) δ : 2.55 (s, 3H, C-CH_3), 6.9-8.1 (m, 5H, Ar-H), 8.9 (d, 1H, Ar-H, o- to both NO_2, J=2.5Hz).

Analysis for : $C_{14}H_{11}N_5O_4$ (313)

Calcd. : C, 53.67; H, 3.51; N, 22.36

Found : C, 54.12; H, 3.85; N, 22.10%.

5(6)-(2,4-Diaminophenyl)aminobenzimidazole (30)

A solution of 28 (5.0 g, 0.016 mol) and Raney-nickel (~0.5 g) in 95% ethanol (100 ml) was shaken with hydrogen under 2.5 kg/cm^2 pressure in a Paar hydrogenator for 24 hr. The catalyst was filtered and solvent was removed in vacuo. The amine was purified by acid-base treatment, yield 2.5 g (62%), m.p.115°.

IR(KBr) cm^{-1} : 3200-3400 (NH,NH_2).

Analysis for : $C_{13}H_{13}N_5$ (239)

Calcd. : C, 65.27; H, 5.44; N, 29.29

Found : C, 65.64; H, 5.12; N, 29.68%.

Under similar reaction condition compound 31 was prepared by reduction of 29 with Raney-nickel and H_2, yield 70%, m.p. $>300^{\circ}$.

IR(KBr) cm^{-1} : 3200-3300(NH,NH_2).

Analysis for : $C_{14}H_{15}N_5$ (253)

Calcd. : C, 66.40; H, 5.91; N, 27.66

Found : C, 66.68; H, 6.22; N, 27.34%.

5(6)-(5-Formamido-1-benzimidazolyl)benzimidazole (32)

A solution of 30 (1.0 g, 0.0041 mol) was refluxed in 98% formic acid (15 ml) for 8 hr. The reaction mixture was cooled and neutralized with dilute sodium hydroxide solution. The solid, thus obtained, was filtered, washed with water, dried and purified over silica gel column using ethyl acetate-benzene (9:1) mixture as eluant, yield 0.74 g (65%), m.p. $>300^{\circ}$.

IR(KBr) cm^{-1} : 1660 (CO).

Mass at m/z : 277 (M^+)

Analysis for : $C_{15}H_{11}N_5O$ (277)

Calcd. : C, 64.98; H, 3.97; N, 25.27

Found : C, 65.36; H, 4.21; N, 25.56%.

Using the similar method 34 was prepared in 62% yield by treating 31 with formic acid.

5(6)-(5-Acetamido-2-methyl-1-benzimidazolyl)benzimidazole (33)

A solution of 30 (1.2 g, 0.005 mol) in glacial acetic acid (15 ml) was refluxed for 8 hr. The reaction mixture was cooled and neutralized with dilute NaOH solution. The solid, thus separated, was filtered, washed with water, dried and purified over silica gel column using ethyl acetate as eluant, yield 1.0 g (66%), m.p. $>300^{\circ}$.

IR(KBr) cm^{-1} : 1680 (CO).

NMR(TFA) δ : 2.02 (s, 3H, $COCH_3$), 2.42 (s, 3H, $C-CH_3$), 6.9-8.0 (m, 6H, Ar-H),

Mass at m/z : 305 (M^+)

Analysis for : $C_{17}H_{15}N_5O$ (305)

Calcd. : C, 66.88; H, 4.91; N, 22.95

Found : C, 66.73; H, 5.25; N, 23.21%.

Similar procedure was employed for the preparation of 35 by reaction of 31 with glacial acetic acid.

6-Nitrobenzthiazole (36)

This compound was prepared by the nitration of benzthiazole (13.5 g, 0.1 mol) in HNO_3 (10.7 ml, d=1.5) and H_2SO_4 (21.5 ml, d=1.84) at 10°, yield 9.0 g (50%), m.p.173° (lit.[26] m.p.174°).

Similarly 37 was obtained by nitration of 2-methyl-

benzthiazole, yield 80%, m.p.164-5° (lit.[27] m.p.165°).

6-Aminobenzthiazole (38)

This was prepared by reduction of 36 (5.0 g, 0.027 mol) in methanol (50 ml) using $SnCl_2$ (25 g) in concentrated HCl (50 ml), yield 3.6 g (86.5%), m.p.83° (lit.[28], m.p. 84-5°).

6-Amino-2-methylbenzthiazole (39)

A solution of hydrazine-hydrate (20.6 g, 0.40 mol) in ethanol (30 ml) was added dropwise to refluxing mixture of 37 (10.0 g, 0.05 mol) and Raney-nickel (~1 g) in ethanol (50 ml). Refluxing was continued for 30 minutes and the reaction mixture filtered in hot. The solvent was removed in vacuo and the resulting solid was crystallized from ethanol, yield 7.0 g (83%), m.p.119-121° (lit.[27] m.p.122°).

IR(KBr) cm^{-1} : 3200, 3300 (NH_2).

NMR($CDCl_3$) δ : 2.92 (s, 3H, C-CH_3), 7.95 (d, 1H, Ar-H, m to NH_2, J=9Hz), 8.28 (dd, 1H, Ar-H, p to -S-, J=3 & 9Hz), 8.7 (d, 1H, Ar-H, o to -S-, J=3Hz)

Analysis for : $C_8H_6N_2O_2S$ (194)

Calcd. : C, 49.48; H, 3.09

Found : C, 49.12; H, 2.74%.

6 -(2,4-Dinitrophenyl)aminobenzthiazole (40)

A solution of 38 (2.5 g, 0.016 mol), 1-chloro-2,4-dinitrobenzene (3.36 g, 0.016 mol) and triethylamine (1.5 g, 0.016 mol) in ethanol (40 ml) was refluxed for 15 hr. The reaction mixture was cooled and the separated pure product was filtered, washed with ethanol (3x20 ml) and dried, yield 4.02 g (80.5%), m.p.201°.

IR(KBr) cm^{-1} : 1315, 1580 (NO_2), 1605 (Arom), 3230 (NH).

Mass at m/z : 316 (M^+)

NMR(DMSO-d_6) δ : 7.08 (d, 1H, Ar-H, m to NO_2, J=9Hz), 7.48 (dd, 1H, Ar-H, p to -S-, J=1.5 & 8.5Hz), 8.06 (d, 1H, Ar-H, o to -S-, J=1.5Hz), 8.11 (d, 1H, Ar-H, m to -S-, J=6Hz), 8.16 (dd, 1H, Ar-H, p to NO_2, J=2.0 & 6.5Hz), 8.8 (d, 1H, Ar-H, o to NO_2, J=2.5Hz), 9.3 (s, 1H, S-CH=N).

Analysis for : $C_{13}H_8N_4O_4S$ (316)

Calcd. : C, 49.46; H, 2.80

Found : C, 49.72; H, 2.52%.

Similarly compound 41 was prepared by reaction of 39 with 1-chloro-2,4-dinitrobenzene in refluxing ethanol, yield 85.5%, m.p.181°.

IR(KBr) cm^{-1} : 1335, 1585 (NO_2), 1620 (Arom), 3280 (NH).

NMR(DMSO-d_6) δ : 2.8 (s, 3H, C-CH_3), 7.16 (d, 1H, Ar-H, m to NO_2, J=9Hz), 7.4 (dd, 1H, Ar-H,

p to -S-, J=2.5 & 9Hz), 7.88 (m, 2H, Ar-H, o & m to -S-), 8.15 (dd, 1H, Ar-H, p to NO_2, J=3 & 9Hz), 9.0 (d, 1H, Ar-H, o to NO_2, J=2.7Hz)

Analysis for : $C_{14}H_{10}N_4O_4S$ (330)

Calcd. : C, 50.90; H, 3.03

Found : C, 50.80; H, 3.36%.

6-(2,4-Diaminophenyl)aminobenzthiazole (42)

To a warm mixture of 40 (2.5 g, 0.008 mol) and Raney-nickel (0.3 g) in THF (15 ml) and ethanol (15 ml) was added dropwise a solution of hydrazine-hydrate (6.6 g, 0.0133 mol) in ethanol (15 ml). When the yellow colour of the solution disappeared, the catalyst was filtered off and product obtained on removal of solvent, was crystallised from ethanol, yield 1.56 g (78%), m.p. 120°.

IR(KBr) cm^{-1} : 3150-3300 (NH_2).

Compound 43 was also obtained by reduction of 41 with hydrazine-hydrate and Raney-nickel in 75% yield m.p.146°.

IR(KBr) cm^{-1} : 3200-3350 (NH_2).

6-(2-Thioxo-5-isothiocyanato-1-benzimidazolyl)benzthiazole (44)

Thiophosgene (0.48 ml, 0.0062 mol) in acetone (50 ml) was added dropwise to a stirred solution of 42

(0.8 g, 0.0031 mol) in acetone (100 ml). Stirring was continued for 4 hr and then reaction mixture refluxed for 2 hr. The separated solid was filtered and the mother liquor was concentrated to get a further crop of product. The combined solid product was crystallized from acetone, yield 0.55 g (54%), m.p.245-46°.

IR(KBr) cm^{-1} : 2040 (NCS).

Analysis for : $C_{15}H_8N_4S_3$ (340)

Calcd. : C, 52.94; H, 2.35

Found : C, 52.62; H, 2.72%.

In similar manner compound 45 was prepared from 43 and thiophosgene in acetone.

2-Methyl-6-[2-carbethoxyamino-5-(N,N'-dicarbethoxy-guanidino)-1-benzimidazolyl]benzthiazole (46)

A solution of 1,3-dicarbethoxy-S-methylisothiourea (0.87 g, 0.0036 mol) in ethanol (30 ml) was added to the solution of 43 (0.5 g, 0.0018 mol) in ethanol (10 ml) and the reaction mixture refluxed for 15 hr. The solvent was removed *in vacuo* and the resulting solid purified on a silica gel column using 10% ethyl acetate in benzene as eluant, yield 0.42 g (42%), m.p.98-100°.

IR(KBr) cm^{-1} : 1720 (C=O).

NMR(TFA) δ : 0.75-1.10 [m, 9H, $(CH_2\underline{CH}_3)_3$], 2.66 (s, 3H, S-C-$\underline{CH}_3$), 3.8-4.1 [m, 6H $(\underline{CH}_2CH_3)_3$], 6.8-7.5 (m, 6H, Ar-H)

Analysis for : $C_{25}H_{27}N_7O_6S$ (546)

Calcd. : C, 54.07; H, 4.88

Found : C, 54.41; H, 4.76%.

6-[5-Formamido-1-benzimidazolyl]benzthiazole (47)

A solution of 42 (0.6 g, 0.0023 mol) in 98% formic acid (30 ml) was refluxed for 8 hr. The reaction mixture was cooled and neutralized with 30% aqueous ammonia. The separated solid was filtered off, dried and subjected to charcoal treatment. It was further purified on a silica gel column using 15% ethyl acetate in benzene as eluant, yield 0.38 g (55%), m.p.235-36°.

IR(KBr) cm^{-1} : 1650 (CO), 3250 (NH).

Mass at m/z : 294 (M^+)

Analysis for : $C_{15}H_{10}N_4OS$ (294)

Calcd. : C, 61.22; H, 3.40

Found : C, 60.86; H, 3.16%.

Compound 49 was prepared similarly from 43 in refluxing 98% formic acid.

6-(5-Acetamido-2-methyl-1-benzimidazolyl)benzthiazole (48)

A solution of 42 (0.6 g, 0.0023 mol) in glacial acetic acid (20 ml) was refluxed for 8 hr. The product was worked-up as above and purified on a silica gel column using benzene as eluant, yield 0.46 g (62%), m.p.241°.

IR(KBr) cm^{-1} : 1675 (CO), 3250 (NH).

NMR(DMSO-d_6) δ : 1.95 (s, 3H, $CO\underline{CH}_3$), 2.32 (s, 3H, $C-\underline{CH}_3$), 6.9 (d, 1H, Ar-$\underline{H}$, $\underline{m}$ to NHAc , J=9Hz), 7.2 (d, 1H, Ar-$\underline{H}$, $\underline{m}$ to -S-, J=9Hz), 7.52 (dd, 1H, Ar-$\underline{H}$, $\underline{p}$ to -S-, J=3 & 9Hz), 7.84 (d, 1H, Ar-$\underline{H}$, $\underline{o}$ to -S-, J=2.5Hz), 8.22 (dd, 2H, Ar-$\underline{H}$, $\underline{o}$ to NHAc, J=3 & 9Hz), 9.38 (s, 1H, N=$C\underline{H}$-S)

Analysis for : $C_{17}H_{14}N_4OS$ (322)

Calcd. : C, 63.35; H, 4.34

Found : C, 63.72; H, 4.42%.

Similarly 50 was prepared from 43 and glacial acetic acid.

2-Methyl-6-(2-nitrobenzoyl)aminobenzthiazole (51)

A solution of 2-nitrobenzoyl chloride (1.12 g, 0.0061 mol) in dry benzene (25 ml) was added dropwise to a stirred solution of 39 (1.0 g, 0.0061 mol) in dry benzene (30 ml) and triethylamine (0.61 g, 0.0061 mol) at room temperature. Stirring was continued for 8 hr. The separated solid was filtered and washed with water (2x10 ml) to remove triethylamine hydrochloride. The product was dried and crystallized from ethanol, yield 1.3 g (72%), m.p.198°.

IR(KBr) cm^{-1} : 1340, 1520 (NO_2), 1640 (CO), 3400 (NH).

NMR(DMSO-d_6) δ : 2.75 (s, 3H, $C\underline{H}_3$), 7.6-8.25 (m, 6H, Ar-$\underline{H}$), 8.5 (d, 1H, Ar-$\underline{H}$, -S-C=$C\underline{H}$-, J=2Hz).

Analysis for : $C_{15}H_{11}N_3O_3S$ (313)

Calcd. : C, 57.89; H, 3.53

Found : C, 58.21; H, 3.18%.

2-Methyl-6-(2-aminobenzoyl)aminobenzthiazole (52)

A mixture of 51 (1.0 g, 0.0032 mol) and Raney-nickel (~ 0.2 g) in ethanol (50 ml) was hydrogenated at 2.5 kg/cm^2 pressure in a Paar hydrogenator for 6 hr. The product was worked-up as usual and crystallized from ethanol, yield 0.72 g (79%), m.p.170°.

IR(KBr) cm^{-1} : 1620 (CO), 3270, 3340 (NH_2).

Mass at m/z : 283 (M^+)

NMR(DMSO-d_6) δ : 2.76 (s, 3H, C-C<u>H</u>$_3$), 6.31 (bs, 2H, N<u>H</u>$_2$), 6.5-7.8 (m, 6H, Ar-<u>H</u>), 8.5 (d, 1H, S-C=C<u>H</u>, J=2Hz)

Analysis for : $C_{15}H_{13}N_3OS$ (283)

Calcd. : C, 63.60; H, 4.52

Found : C, 63.48; H, 4.32%.

2-Methyl-6-(2-isothiocyanatobenzoyl)aminobenzthiazole (53)

A solution of thiophosgene (0.054 ml, 0.0007 mol) in chloroform (10 ml) was added dropwise to a stirred solution of 52 (0.2 g, 0.0007 mol) in glacial acetic acid (4 ml) and 10% HCl (5 ml) at room temperature. Stirring was continued for 1 hr. The chloroform layer was washed with water, dried (Na_2SO_4) and concentrated to get a solid

which was washed with pet. ether, yield 0.08 g (38%), m.p.185°.

IR(KBr) cm^{-1} : 1660 (CO), 2090 (NCS).

2-Methyl-6-(2-thioxo-4-oxo-3-quinazolinyl)benzthiazole (54)

A solution of thiophosgene (0.13 ml, 0.0015 mol) in acetone (20 ml) was added dropwise to a stirred solution of 53 (0.5 g, 0.0018 mol) in acetone (50 ml) at room temperature. Stirring was continued for 6 hr and the solid separated was filtered and crystallized from ethanol, yield 0.35 g (68%), m.p. >300°.

IR(KBr) cm^{-1} : 1680 (CO), 3400 (NH).

Mass at m/z : 325 (M^+)

Analysis for : $C_{16}H_{11}N_2OS_2$ (325)

Calcd. : C, 58.00; H, 3.32

Found : C, 58.35; H, 3.56%.

5-Chloro-2-nitroacetanilide (56)

m-Chloroacetanilide 55 (64.0 g, 0.38 mol) was nitrated by concentrated HNO_3 (27.5 ml, d=1.5) in acetic acid-acetic anhydride mixture, yield 44 g (58.6%), m.p. 117-18° (lit.[29] m.p.117-18°).

3,3'-Diamino-4,4'-dinitrodiphenyl sulfide (57)

A solution of sodium sulfide (5.6 g, 0.024 mol) in 50% aqueous ethanol (20 ml) was added dropwise to a stirred solution of 56 (10.0 g, 0.046 mol) in ethanol (60 ml) and

the reaction mixture was refluxed for 12 hr on a water bath. The solid which came out on cooling the reaction mixture was filtered, washed with 50% aqueous ethanol, dried and purified by column chromatography using silica gel and benzene-ethylacetate (2:1) as eluant, yield 3.6 g (38.5%), m.p.195°.

IR(KBr) cm^{-1}	: 1300, 1550 (NO_2), 1600 (Arom), 3280, 3400 (NH_2).
Mass at m/z	: 306 (M^+)
NMR($CDCl_3$ + $DMSO-d_6$) δ	: 6.37 (dd, 2H, Ar-H, p to NH_2, J=2.5 & 8Hz), 6.87 (d, 2H, Ar-H, o to NH_2, J=3Hz), 7.2 (s, 4H, 2xNH_2), 7.82 (d, 2H, Ar-H, o to NO_2, J=9Hz)
Analysis for	: $C_{12}H_{10}N_4O_4S$ (306)
Calcd.	: C, 47.05; H, 3.26; N, 18.30
Found	: C, 47.50; H, 3.48; N, 17.95%.

3,3'-Diacetamido-4,4'-dinitrodiphenyl sulfide (58)

A mixture of 57 (1.0 g, 0.0032 mol) in acetic anhydride (2 ml) and glacial acetic acid (10 ml) was refluxed for 4 hr. The reaction mixture was cooled, the separated solid was filtered, washed successively with 10% $NaHCO_3$ solution and water. Another crop was obtained on dilution of filtrate with water. The combined product was recrystallised from acetone, yield 1.0 g (80%), m.p.175°.

IR(KBr) cm^{-1} : 1320, 1580 (NO_2), 1600 (Arom), 1700 (CO), 3300 (NH).

NMR($CDCl_3$ + DMSO-d_6) δ : 2.1 (s, 6H, 2x$COCH_3$), 7.05 (dd, 2H, Ar-H, p to NHAc, J=2 & 9Hz), 7.92 (d, 2H, Ar-H, o to NO_2, J=9Hz), 8.14 (d, 2H, Ar-H, o to NHAc, J=3Hz)

Analysis for : $C_{16}H_{14}N_4O_6S$ (390)

Calcd. : C, 49.23; H, 3.59

Found : C, 49.50; H, 3.86%.

3,3',4,4'-Tetra-aminodiphenyl sulfide (59)

A hot solution of 57 (1.4 g, 0.0032 mol) in acetone (20 ml) and aqueous ammonia (25 ml) was mixed with hot solution of $FeSO_4$ (7.0 g) in water (20 ml) and aqueous ammonia solution (30 ml) and the reaction mixture heated on water bath for 30 minutes. Then product was extracted with ethyl acetate (5x20 ml), combined extracts dried (Na_2SO_4) and solvent removed *in vacuo* to get crude product, yield 0.6 g (75%), This was used as such in further steps.

5,5'-Dibenzimidazolyl sulphide (60)

A solution of 59 (0.6 g, 0.0023 mol) in 98% formic acid was refluxed for 5 hr on water bath. The reaction mixture was cooled, neutralized with aqueous ammonia solution, extracted with methylene chloride (2x30 ml), dried (Na_2SO_4) and solvent removed *in vacuo*. The residual solid was further purified by charcoal treatment, yield

0.45 g (70%), m.p.260-2°.

IR(KBr) cm^{-1} : 1605 (Arom), 3350 (NH).

Mass at m/z : 266 (M^+)

Analysis for : $C_{14}H_{10}N_4S$ (266)

Calcd. : C, 63.15; H, 3.75

Found : C, 63.50; H, 4.10%.

Similarly 61 was prepared by treating 59 with refluxing acetic acid.

2,2'-Dicarbomethoxyamino-5,5'-dibenzimidazolyl sulphide (62)

A solution of 59 (0.5 g, 0.002 mol) and 1,3-dicarbomethoxy-S-methylisothiourea (0.85 g, 0.0042 mol) in ethanol (50 ml) was refluxed overnight. The reaction mixture was cooled. The separated solid was filtered, washed with ethanol (3x20 ml), water (3x20 ml) and dried. The product was then crystallized from acetic acid-water, yield 0.53 g (64%), m.p. >280°.

IR(KBr) cm^{-1} : 1600 (Arom), 1710 (CO), 2700-2800 (C-H), 3300 (NH).

NMR(TFA) δ : 3.6 (s, 6H, 2xOC<u>H</u>$_3$), 7.1-7.2 (m, 6H, Ar-<u>H</u>)

Analysis for : $C_{18}H_{16}N_6O_4S$ (412)

Calcd. : C, 52.42; H, 3.88; N, 20.38

Found : C, 52.80; H, 3.52; N, 20.72%.

Similarly 63 was prepared by reaction of 59 with 1,3-dicarbethoxy-S-methylisothiourea in refluxing ethanol.

4,4'-Dichloro-3,3'-dinitrodiphenyl sulfone (65)

This was obtained by nitration of 4,4'-dichlorodiphenyl sulfone 64 (6.0 g, 0.021 mol) using H_2SO_4-HNO_3 mixture at 60°. The product isolated by pouring it into water, yield 6.7 g (86%), m.p.201° (lit.[30] m.p.201-202°).

4,4'-Diamino-3,3'-dinitrodiphenyl sulfone (66)

Ammonia gas was passed in a solution of 65 (5.0 g, 0.013 mol) in DMSO at 140° for 5 hr. The reaction mixture cooled and diluted with water. The separated solid was filtered, washed with water and dried, yield 3.52 g (80%), m.p.286° (lit.[31] m.p.287°).

3,3'-Diamino-4,4'-dinitrodiphenyl sulfone (67)

To a hot solution of 3,3'-diamino-4,4'-dinitrodiphenyl sulfide 57 (0.5 g, 0.0016 mol) in 80% aqueous acetic acid (250 ml) was added $KMnO_4$ (0.5 g) in small portions during 30 minutes with constant stirring. Stirring was continued for 5 hr at room temperature and excess $KMnO_4$ was decomposed with H_2O_2 solution in cold. Then the reaction mixture was diluted with water (250 ml). The separated solid was filtered, washed with water (3x20 ml) and dried, yield 0.2 g (36.36%), m.p.276-8°.

IR(KBr) cm^{-1} : 1150 (SO_2), 1320, 1560 (NO_2), 1620 (Arom), 3300, 3400 (NH_2).

Mass at m/z : 338 (M^+)

NMR(DMSO-d_6) δ : 6.9 (dd, 2H, Ar-H, p to NH_2, J=2.5 & 9Hz), 7.65 (d, 2H, Ar-H, o to NH_2, J=2.5Hz), 8.16 (d, 2H, Ar-H, o to NO_2, J=9Hz).

Analysis for : $C_{12}H_{10}N_4O_6S$ (338)

Calcd. : C, 42.60; H, 2.95; N, 16.56

Found : C, 43.04; H, 3.16; N, 16.28%.

3,3',4,4'-Tetra-aminodiphenyl sulfone (68)

To a warm solution of 66 (5.0 g, 0.015 mol) in THF-ethanol (1:1, 200 ml) and Raney-nickel (~ 1.5 g), was added dropwise a solution of hydrazine-hydrate (5.75 ml, 0.12 mol) in ethanol (25 ml) during 30 minutes. After addition was complete, the reaction mixture was refluxed for 3 hr on a water bath. The catalyst was filtered and the product was worked up as usual and purified by acid-base treatment, yield 2.9 g (72%), m.p.148-52°.

IR(KBr) cm^{-1} : 1125 (SO_2), 1620 (Arom), 3200-3350 (NH_2).

5,5'-Dibenzimidazolyl sulphone (69)

A solution of 68 (1.0 g, 0.0036 mol) in 98% formic acid (20 ml) was heated for 5 hr on a water bath. The

reaction mixture was cooled, neutralized with 30% aqueous ammonia solution. The separated solid was filtered, washed with water (3x20 ml), dried and purified over a silica gel column using ethyl acetate as eluant, yield 0.76 g (71%), m.p. $>300^{\circ}$.

IR(KBr) cm^{-1} : 1145 (SO_2), 1620 (Arom), 3400 (NH).

Mass at m/z : 298 (M^+)

NMR(DMSO-d_6) δ : 7.65 (bs, 6H, Ar-H), 8.2 (s, 2H, 2xN=CH-N).

Similarly 70 was prepared from 68 and acetic acid.

2,2'-Dicarbomethoxyamino-5,5'-dibenzimidazolyl sulphone(71)

A solution of 68 (1.0 g, 0.0036 mol) and 1,3-dicarbomethoxy-S-methylisothiourea (1.5 g, 0.0072 mol) in ethanol (30 ml) was refluxed for 15 hr. The reaction mixture was worked-up as usual and recrystallized from acetic acid-water, yield 0.98 g (61.8%), m.p. $>280^{\circ}$.

IR(KBr) cm^{-1} : 1715 (CO), 2700-2900 (C-H), 3350 (NH).

NMR(TFA) δ : 3.6 (bs, 6H, 2xOC$\underline{H}_3$), 7.5-7.8 (m, 6H, Ar-H)

Analysis for : $C_{18}H_{16}N_6O_6S$ (444)

Calcd. : C, 48.64; H, 3.60; N, 18.91

Found : C, 48.28; H, 4.06; N, 19.32%.

Similarly compound 72 was prepared from 68 and 1,3-dicarbethoxy-S-methylisothiourea in refluxing ethanol.

4-Acetamido-3-nitrobenzoic acid (74)

This compound was prepared by nitration of 4-acetamidobenzoic acid 73 (50 g, 0.27 mol) with HNO_3, (200 ml, d=1.5), yield 52 g (87%), m.p.220° (lit.[32] m.p.221°.

4-Amino-3-nitrobenzoic acid (75)

Hydrolysis of 74 (10.0 g, 0.044 mol) in concentrated HCl (30 ml) gave the required product, yield 6.15 g (76%), m.p.282-83° (lit.[32] m.p.284°).

3,4-Diaminobenzoic acid (76)

Catalytic hydrogenation of 75 (1.0 g, 0.0054 mol) using Raney-nickel (about 200 mg) in ethanol and H_2 at 3 kg/cm^2 pressure in a Paar hydrogenator gave the product by usual work-up, yield 0.6 g (72.3%), m.p.215-16° (lit.[33] m.p.215-18°).

2-Carbethoxyaminobenzimidazole-5(6)-carboxylic acid (78)

A mixture of 76 (1.0 g, 0.0065 mol) and 1,3-dicarbethoxy-S-methylisothiourea (1.53 g, 0.0065 mol) in ethanol (30 ml) was refluxed for 12 hr. The product was worked-up as usual and recrystallised from acetic acid-water, yield 1.0 g (62.5%), m.p. >280°.

IR(KBr) cm^{-1} : 1595 (Arom), 1700 (CO), 2800-2900 (C-H), 3350 (NH).

NMR(TFA) δ : 1.0 (t, 3H, $CH_2\underline{CH}_3$, J=7Hz), 4.08 (q, 2H, $\underline{CH}_2CH_3$, J=7Hz), 7.2-8.05 (m, 3H, Ar-H)

Analysis for : $C_{11}H_{11}N_3O_4$ (249)

Calcd. : C, 53.01; H, 4.41

Found : C, 53.42; H, 4.68%.

Similarly compound 77 was prepared from 76 and 1,3-dicarbomethoxy-S-methylisothiourea in refluxing ethanol, yield (56%), m.p. 300°.

IR(KBr) cm^{-1} : 1600 (Arom), 1720 (CO), 2600-2700 (C-H), 3350 (NH).

NMR(TFA) δ : 3.52 (s, 3H, $O\underline{CH}_3$), 7.2-8.2 (m, 3H, Ar-H).

Analysis for : $C_{10}H_9N_3O_4$

Calcd. : C, 51.06; H, 3.82

Found : C, 50.60; H, 4.12%.

4,4'-Dichlorobenzophenone (83)

4-Chlorobenzoyl chloride (6.0 g, 0.0034 mol) was treated with chlorobenzene (3.8 g, 0.033 mol) in presence of $AlCl_3$ (10.0 g) in dry CS_2 (50 ml), yield 4.6 g (54.8%), m.p.145° (lit.[34] m.p.144-46°).

4,4'-Dichloro-3,3'-dinitrobenzophenone (84)

This compound was prepared by nitration of 83 (6.0 g, 0.023 mol) in H_2SO_4 (24 ml, d=1.84) and HNO_3 (24 ml, d=1.42) at 60°. The product was worked up in usual manner and

crystallized from ethanol, yield 6.75 g (82.8%), m.p. 144-5° (lit.[35] m.p.146.5°).

4,4'-Diamino-3,3'-dinitrobenzophenone (85)

NH_3 gas was bubbled to a solution of 84 (1.1 g, 0.0032 mol) in DMSO (20 ml) at 140° for 4 hr. The product was isolated on dilution with water, yield 0.9 g (92.7%), m.p.121° (lit.[36] m.p.121°).

IR(KBr) cm^{-1} : 1320, 1530 (NO_2), 1600 (Arom), 1625, (CO), 3380, 3500 (NH_2).

NMR(DMSO-d_6) δ : 7.05 (d, 2H, Ar-H, o to NH_2, J=9Hz), 7.7 (dd, 2H, Ar-H, p to NO_2, J=2 & 9Hz), 8.26 (d, 2H, Ar-H, o to NO_2, J=2Hz).

3,3',4,4'-Tetra-aminobenzophenone (86)

A mixture of 85 (3.02 g, 0.01 mol) and Raney-nickel (about 0.5 g) in ethanol (100 ml) was shaken with H_2 at 3.5 kg/cm^2 in a Paar hydrogenator for 16 hr and product worked-up in usual manner, yield 2.0 g (82.6%), m.p.217° (lit.[37] m.p.217°).

IR(KBr) cm^{-1} : 1625 (CO), 3320-3380 (NH_2).

NMR(DMSO-d_6) δ : 6.46 (d, 2H, Ar-H, J=9Hz), 6.75 (dd, 2H, Ar-H, J=2 & 9Hz), 6.9 (d, 2H, Ar-H, J=2Hz).

2,2'-Dicarbomethoxyamino-5,5'-dibenzimidazolyl ketone (81)

A solution of 86 (0.5 g, 0.002 mol) and 1,3-dicarbomethoxy-S-methylisothiourea (0.86 g, 0.0041 mol) in ethanol (20 ml) was refluxed for 12 hr. The product was isolated in usual manner and recrystallised from acetic acid-water, yield 0.55 g (65.5%), m.p. $>280^{\circ}$.

IR(KBr) cm^{-1} : 1590 (Arom), 1630, 1705 (CO), 2700-2900 (C-H), 3300 (NH).

NMR(TFA) δ : 3.62 (s, 6H, 2xOCH_3), 7.4-7.85 (m, 6H, Ar-H)

Analysis for : $C_{19}H_{16}N_6O_5$ (408)

Calcd. : C, 55.88; H, 3.92

Found : C, 56.30; H, 3.65%.

Similarly 82 was prepared from 86 and 1,3-dicarbethoxy-S-methylisothiourea in ethanol.

5,5'-Dibenzimidazolyl ketone (88)

A solution of 86 (0.5 g, 0.002 mol) in 98% formic acid (15 ml) was heated for 3 hr on a water bath. The reaction mixture was cooled, neutralized with aqueous ammonia solution. The solid thus separated was filtered, washed with water, dried, yield 0.4 g (74%), m.p. 280°.

IR(KBr) cm^{-1} : 1620 (Arom), 1645 (CO).

Mass at m/z : 262 (M^+)

NMR(DMSO-d_6) δ : 7.5-8.5 (m, 8H, Ar-H & N=CH-N).

Analysis for : $C_{15}H_{10}N_4O$ (262)

Calcd. : C, 68.70; H, 3.81

Found : C, 68.32; H, 4.12%.

Similarly 89 was prepared from 86 and glacial acetic acid.

3,3',4,4'-Tetra-aminodiphenyl methane (87)

A mixture of 85 (3.0 g, 0.01 mol), 99% hydrazine-hydrate (3 ml, 0.08 mol) and KOH (3 g) was heated in steel bomb at 170° for 24 hr. The reaction mixture was cooled, the separated pure solid (1.2 g) was filtered, washed with water and dried. The filtrate was extracted with ethyl acetate (3x20 ml), washed with water (3x20 ml), dried (Na_2SO_4) and solvent removed *in vacuo*. The product crystallised from ethanol, yield 1.45 g (64%), m.p.136° (lit.[37] m.p.137°).

IR(KBr) cm^{-1} : 1600 (Arom), 3300-3500 (NH_2).

NMR($CDCl_3$ + DMSO-d_6) δ : 3.56 (s, 2H, CH_2), 6.24-6.42 (m, 6H, Ar-H).

2,2'-Dicarbomethoxyamino-5,5'-dibenzimidazolylmethane (90)

A solution of 87 (0.8 g, 0.0035 mol) and 1,3-dicarbomethoxy-S-methylisothiourea (1.45 g, 0.0070 mol) in ethanol (30 ml) was refluxed for 15 hr. The product was isolated in usual manner and recrystallised from acetic acid-water, yield 0.86 g (62.7%), m.p. >300°.

IR(KBr) cm^{-1} : 1710 (CO), 2600-2950 (C-H)
3300 (NH).

NMR(TFA) δ : 3.6 (s, 6H, 2xOC<u>H</u>$_3$), 3.86 (s, 2H, -C<u>H</u>$_2$-), 6.96-7.15 (m, 6H, Ar-<u>H</u>)

Analysis for : $C_{19}H_{18}N_6O_4$ (394)

Calcd. : C, 57.86; H, 4.56

Found : C, 58.22; H, 4.34%.

In similar manner <u>91</u> was prepared by treating <u>87</u> with 1,3-dicarbethoxy-S-methylisothiourea in refluxing ethanol.

5,5'-Dibenzimidazolylmethane (<u>92</u>)

<u>87</u> (0.4 g, 0.0017 mol) was heated in 98% formic acid for 2 hr on water bath. The product was worked-up as usual and finally crystallized from water, yield 0.30 g (70%), m.p.120-2°.

IR(KBr) cm^{-1} : 1600 (Arom), 3100-3350 (NH).

NMR(DMSO-d_6) δ : 4.1 (s, 2H, C<u>H</u>$_2$), 6.9-7.6 (m, 6H, Ar-<u>H</u>), 8.12 (s, 2H, 2xN=C<u>H</u>-N)

Analysis for : $C_{15}H_{12}N_4$ (248)

Calcd. : C, 72.58; H, 4.83

Found : C, 72.42; H, 5.12%.

Using the above method, <u>93</u> was prepared by refluxing <u>87</u> in glacial acetic acid.

4-Acetoxyacetanilide (95)

This compound was prepared by acetylation of 4-acetamidophenol 94 (15 g, 0.1 mol) by acetic anhydride in glacial acetic acid using literature method, yield 15.44 g (80%), m.p.148-52° (lit.[38] m.p.151-4°).

4-Acetoxy-2-nitroacetanilide (96)

Nitration of 95 (10.0 g, 0.051 mol) in HNO_3 (10 ml, d=1.5) was done under cooling and stirring. The reaction mixture was poured on ice and product filtered, dried and recrystallized from 50% aqueous ethanol, yield 7.8 g (64%), m.p.142-4° (lit.[38] m.p.145-46°).

4-Acetamido-3-nitrophenol (97)

To a hot suspension of 96 (1.0 g, 0.0042 mol) in ethanol (10 ml) was added 10% aqueous solution of KOH (0.25 g) and mixture heated for 15 minutes on water bath. Solvent removed and the residue acidified with dilute HCl. The crystals separated on cooling, were filtered, washed and dried, yield 0.70 g (85.3%), m.p.218° (lit.[38] m.p.218-20°).

5-(4-Acetamidophenoxy)-2-nitroacetanilide (101)

A solution of potassium-4-acetamidophenoxide (0.5 g, 0.0031 mol) and 5-chloro-2-nitroacetanilide (56) (0.67 g, 0.0031 mol) in dry DMF (30 ml) was refluxed for

24 hr. The reaction mixture was cooled, diluted with water (100 ml) and extracted with ethyl acetate (3x25 ml). The combined extract was dried (Na_2SO_4), solvent removed *in vacuo* and the residue crystallised from ethanol, yield 0.48 g (48%), m.p.178°.

IR(KBr) cm^{-1} : 1320, 1520 (NO_2), 1600 (Arom), 1660, 1700 (CO), 3250 (NH).

NMR(DMSO-d_6) δ : 2.06 (s, 6H, 2x$COCH_3$), 6.8 (dd, 1H, Ar-H, p to NHAc, J=2.5 & 9Hz), 7.06 (d, 2H, Ar-H, m to NHAc, J=9Hz), 7.42 (d, 1H, Ar-H, o to NHAc (m to NO_2), J=2Hz), 7.68 (d, 2H, Ar-H, o to NHAc, J=9Hz), 8.0 (d, 1H, Ar-H, o to NO_2, J=9Hz), 10.0 (s, 1H, NHCO)

Analysis for : $C_{16}H_{15}N_3O_5$ (329)

Calcd. : C, 58.05; H, 4.55

Found : C, 58.42; H, 4.35%.

4,4'-Dinitrodiphenyl ether (102)

A mixture of potassium 4-nitrophenoxide (20.0 g, 0.113 mol) and 1-chloro-4-nitrobenzene (17.8 g, 0.113 mol) was refluxed in dry DMF (50 ml) for 40 hr and worked-up as usual, yield 12.5 g (42.6%), m.p.142° (lit.[39] m.p. 142-3°).

4,4'-Diaminodiphenyl ether (103)

This was obtained by reduction of 102 (10.0 g, 0.038 mol) by hydrazine hydrate and Raney-nickel by the method as described for 39, yield 5.5 g (72.3%), m.p. 185-6° (lit.[39] m.p.186-7°).

4,4'-Diacetamidodiphenyl ether (104)

Acetylation of 103 (2.0 g, 0.01 mol) by acetic anhydride in an usual manner gave 2.2 g of the product, yield 77.4%, m.p.222°.

IR(KBr) cm^{-1} : 1660 (CO), 3280 (NH).

NMR(DMSO-d_6) δ : 2.0 (s, 6H, 2x$COCH_3$), 6.8 (d, 4H, Ar-H, m to NHAc, J=9Hz), 7.45 (d, 4H, Ar-H, o to NHAc, J=9Hz), 9.76 (s, 2H, 2xNHCO)

Analysis for : $C_{16}H_{16}N_2O_3$ (284)

Calcd. : C, 67.60; H, 5.63

Found : C, 67.25; H, 5.46%.

4,4'-Diacetamido-3,3'-dinitrodiphenyl ether (105)

To an ice cooled (10°) solution of 104 (5.0 g, 0.017 mol) in glacial acetic acid (30 ml) was added dropwise fuming HNO_3 (6.24 ml, d=1.5) during 20-30 minutes with stirring. The stirring was continued for 2 hr during cooling and then the mixture poured on crushed ice. The solid separated was filtered, washed with water (3x30 ml), dried and recrystallized from ethanol, yield

5.4 g (82.1%), m.p.212°.

IR(KBr) cm^{-1} : 1320, 1500 (NO_2), 1670 (CO), 3240 (NH).

NMR($CDCl_3$) δ : 2.2 (s, 6H, 2x$COCH_3$), 7.18 (dd, 2H, Ar-H, p to NO_2, J=3 & 9Hz), 7.65 (d, 2H, Ar-H, o to NO_2, J=3Hz), 8.65 (d, 2H, Ar-H, m to NO_2, J=9Hz)

Analysis for : $C_{16}H_{14}N_4O_7$ (374)

Calcd. : C, 51.33; H, 3.74; N, 14.97

Found : C, 51.56; H, 3.28; N, 15.32%.

4,4'-Diamino-3,3'-dinitrodiphenyl ether (106)

105 (4.0 g, 0.0106 mol) was refluxed in 50% HCl (50 ml) for 5 hr. The reaction mixture was cooled, neutralized with aqueous ammonia and the separated solid was filtered, washed with water (3x20 ml) and dried. The product was recrystallized from ethanol, yield 2.8 g (90%), m.p.176°.

IR(KBr) cm^{-1} : 1320, 1510 (NO_2), 1600 (Arom), 3360, 3500 (NH_2).

NMR($CDCl_3$) δ : 5.85 (hump, 4H, 2xNH_2), 6.65 (d, 2H, Ar-H, o to NH_2, J=9Hz), 7.0 (dd, 2H, Ar-H, p to NO_2, J=3 & 9Hz), 7.51 (d, 2H, Ar-H, o to NO_2, J=3Hz).

Analysis for : $C_{12}H_{10}N_4O_5$ (290)

Calcd. : C, 49.65; H, 3.44; N, 19.31

Found : C, 49.26; H, 3.82; N, 19.68%.

3,3',4,4'-Tetra-aminodiphenyl ether (107)

To a warm solution of 106 (1.0 g, 0.0034 mol) in ethanol-THF (1:1, 30 ml) and Raney-nickel (~0.2 g) was added dropwise hydrazine-hydrate (1.37 g, 0.0272 mol) in ethanol (10 ml). After the addition was complete, the reaction mixture was heated till it was colourless. The catalyst was filtered off, washed with ethanol and solvent removed to get oily product, yield 0.6 g (76%). This was not purified and used as such for next step.

2,2'-Dicarbomethoxyamino-5,5'-dibenzimidazolyl oxide (110)

A mixture of 107 (0.6 g, 0.0026 mol) and 1,3-dicarbomethoxy-S-methylisothiourea (1.74 g, 0.0052 mol) in ethanol (30 ml) was refluxed for 12-15 hr. The product was worked-up as usual and recrystallized from DMSO, yield 0.63 g (62%), m.p. $>300^{o}$.

IR(KBr) cm^{-1} : 1600 (Arom), 1710 (CO), 2700-2900 (C-H), 3350 (NH).

NMR(TFA) δ : 3.58 (s, 6H, 2xOC$\underline{H}_3$), 6.7-7.2 (m, 6H, Ar-$\underline{H}$)

Analysis for : $C_{18}H_{16}N_6O_5$ (396)

Calcd. : C, 52.02; H, 4.04,

Found : C, 51.68; H, 4.44%.

In similar manner compound 111 was prepared from 107 and 1,3-dicarbethoxy-S-methylisothiourea in ethanol while 108 and 109 were obtained by refluxing 107 in formic and acetic acids respectively.

1,2-Di-(3-amino-4-nitrophenylthio)ethane (112)

A solution of ethanedithiol (1.96 ml, 0.017 mol) and KOH (1.94 g, 0.034 mol) in ethanol (20 ml) was stirred at room temperature for 30 minutes. To this stirred solution, was added a solution of 5-chloro-2-nitroaniline 98 (6.0 g, 0.034 mol) in ethanol (25 ml). The reaction mixture was refluxed for 2 hr on a water bath. The separated solid was filtered after cooling the reaction mixture, washed with ethanol (3x20 ml) and water (3x20 ml) and dried, yield 3.0 g (46.5%), m.p.265-6° (d).

IR(KBr) cm^{-1} : 1320, 1560 (NO_2), 1620 (Arom), 3350, 3475 (NH_2).

NMR(DMSO-d_6) δ : 3.28 (s, 4H, S-(CH_2)$_2$-S), 6.45 (dd, 2H, Ar-H, p to NH_2, J=3 & 9Hz), 6.84 (d, 2H, Ar-H, o to NH_2, J=3Hz), 7.34 (s, 4H, 2xNH_2 exchangeable in D_2O), 7.79 (d, 2H, Ar-H, o to NO_2, J=9Hz).

1,2-Di-(3,4-diaminophenylthio)ethane (114)

A suspension of 112 (1.0 g, 0.0027 mol) and 10% Pd/C (~ 200 mg) in ethanol (200 ml) was shaken in Paar hydrogenator at 3.5 kg/cm^2 pressure for 10 hr. The catalyst

was filtered and washed with ethanol (2x10 ml). Solvent was removed from filtrate *in vacuo* to get crude tetra-amine which was crystallised from ethanol, yield 0.2 g (24%), m.p. 115°.

IR(KBr) cm^{-1} : 1605 (Arom), 3200, 3300 (NH_2).

Mass at m/z : 306 (M^+).

1,2-Di-(2-carbomethoxyaminobenzimidazolyl-5(6)-thio) ethane (115)

A solution of 114 (0.4 g, 0.0013 mol) and 1,3-dicarbomethoxy-S-methylisothiourea (0.54 g, 0.0026 mol) in ethanol (25 ml) was refluxed for 15 hr. The compound was isolated as usual, yield 0.35 g (57.3%), m.p. > 280°.

IR(KBr) cm^{-1} : 1600 (Arom), 1715 (CO), 2700-2900 (C-H), 3340 (NH).

NMR(TFA) δ : 2.72 (s, 4H, S-($C\underline{H}_2$)$_2$-S), 3.58 (s, 6H, 2x$OC\underline{H}_3$), 7.08-7.22 (m, 6H, Ar-H)

Analysis for : $C_{20}H_{20}N_6O_4S_2$ (472)

Calcd. : C, 50.84; H, 4.23

Found : C, 51.22; H, 4.64%.

Similarly 116 was prepared from 114 and 1,3-dicarbethoxy-S-methylisothiourea in refluxing ethanol.

4-Chloro-3-nitrobenzoyl chloride (117) and 4-acetamido-3-nitrobenzoyl chloride (118)

These were prepared by refluxing 4-chloro-3-nitrobenzoic acid and 4-acetamido-3-nitrobenzoic acid with thionyl chloride in dry benzene in 70 and 72% yields. The acid chlorides were used as such in next step.

1,4-Di-(4-chloro-3-nitrobenzoyl)piperazine (119)

A solution of anhydrous piperazine (0.5 g, 0.0058 mol) in dry benzene (20 ml)was added dropwise to a stirred solution of 4-chloro-3-nitrobenzoyl chloride 117 (2.56 g, 0.0116 mol) in dry benzene (100 ml). Stirring was continued for 5 hr at room temperature. The separated solid was filtered, washed with benzene (3x10 ml), water (5x10 ml) and dried, yield 2.2 g (83.6%), m.p.224°.

IR(KBr) cm^{-1} : 1340, 1535 (NO_2), 1640 (NCO), 2670, 2920 (C-H).

NMR(DMSO-d_6) δ : 3.47 (s, 8H, 4xN-CH_2), 7.6-7.8 (m, 4H, Ar-H, m & p to NO_2), 8.0 (d, 2H, Ar-H, o to NO_2, J=3Hz)

Analysis for : $C_{18}H_{14}N_4O_6Cl_2$ (453)

Calcd. : C, 47.68; H, 3.09

Found : C, 47.56; H, 3.15%.

Similarly 120 was prepared from 4-acetamido-3-nitro benzoyl chloride (118) and anhydrous piperazine in dry benzene, yield 88.1%, m.p.250°.

IR(KBr) cm^{-1} : 1360, 1540 (NO_2), 1650 (NCO), 1670 (NHCO), 2700, 2950 (C-H), 3300 (NH).

NMR(TFA) δ : 2.02 (s, 6H, 2x$COCH_3$), 3.6 (s, 8H, N-(CH_2)$_4$), 7.2-8.25 (m, 6H, Ar-H)

Analysis for : $C_{22}H_{22}N_6O_8$ (498)

Calcd. : C, 53.01; H, 4.41

Found : C, 52.65; H, 4.86%.

1,4-Di-(4-amino-3-nitrobenzoyl)piperazine (121)

To a stirred suspension of 120 (4.6 g, 0.0092 mol) in ethanol (100 ml) was added dropwise at room temperature a 10% aqueous solution of KOH in small fractions till all the compound went into the solution. Stirring continued for 5 hr at room temperature, the separated solid was filtered, washed with ethanol (3x20 ml), water (3x20 ml), dried and crystallised from DMSO-water, yield 2.4 g (62.8%), m.p.280° (d).

IR(KBr) cm^{-1} : 1350, 1520 (NO_2), 1600 (Arom), 1640 (-NCO).

NMR(DMSO-d_6) δ : 3.55 (s, 8H, N-(CH_2)$_4$), 6.98 (d, 2H, Ar-H, m to NO_2, J=8Hz), 7.42 (dd, 2H, Ar-H, p to NO_2, J=2 & 9Hz), 7.5-7.7 (bs, 4H, 2xNH_2), 7.95 (d, 2H, Ar-H, o to NO_2, J=2Hz)

Analysis for : $C_{18}H_{18}N_6O_6$ (414)

Calcd. : C, 52.17; H, 4.34

Found : C, 52.53; H, 4.68%.

1,4-Di-(3,4-diaminobenzoyl)piperazine (122)

A suspension of 121 (1.0 g, 0.0024 mol) in ethanol-THF (1:1, 200 ml) and Raney-nickel (~0.3 g) was shaken on a Paar hydrogenator at 3.5 kg/cm^2 pressure for 12 hr. The catalyst was filtered off and washed with hot alcohol-THF (3x25 ml). The filtrate was concentrated and the residue crystallized from ethanol, yield 0.45 g (53%), m.p.266-7°.

IR(KBr) cm^{-1} : 1590 (Arom), 1620 (CO), 3180, 3240 (NH_2).

Mass at m/z : 354 (M^+).

1,4-Di-(2-carbomethoxyaminobenzimidazolyl-5(6)-carbonyl)piperazine (123)

A solution of 122 (0.3 g, 0.008 mol) and 1,3-dicarbomethoxy-S-methylisothiourea (0.35 g, 0.0017 mol) in ethanol (25 ml) was refluxed for 15 hr. The reaction mixture was cooled, the solid thus separated was filtered, washed with water (3x10 ml), ethanol (3x10 ml) and dried, yield 0.18 g (41%), m.p. >280°.

IR(KBr) cm^{-1} : 1720 (CO), 2750-2950 (C-H), 3460 (NH).

NMR(TFA) δ : 3.35 (hump, 8H, N-(CH_2)$_4$), 3.6 (s, 6H, 2xOCH_3), 7.0-7.5 (m, 6H, Ar-H)

Analysis for : $C_{24}H_{24}N_8O_6$ (520)

Calcd. : C, 55.38; H, 4.61; N, 21.53

Found : C, 54.95; H, 4.88; N, 21.32%.

In similar manner 124 was prepared from 101 and 1,3-dicarbethoxy-S-methylisothiourea.

4-Amino-3-nitrobiphenyl (125)

4-Acetamido-3-nitrobiphenyl (25.6 g, 0.1 mol) was suspended in boiling ethanol (100 ml) and potassium hydroxide (12.8 g) in water (12 ml) was added. The reaction mixture was heated on water bath for 25 minutes and cooled. Crystals separated after 10 minutes which were filtered and purified by washing with 30% aqueous ethanol, yield 18.5 g (86.4%), m.p.168° (lit.[40] m.p.167-9°).

3,4-Diaminobiphenyl (126)

This was prepared by reduction of 125 using hydrazine-hydrate and Raney-nickel and worked-up as usual, yield 65%, m.p.103° (lit.[41] m.p.102°-103°).

Ethyl 5(6)-phenylbenzimidazole-2-carbamate (127)

A mixture of 126 (1.0 g, 0.0054 mol) and 1,3-dicarbethoxy-S-methylisothiourea (1.26 g, 0.006 mol) in ethanol (50 ml) was refluxed for 12 hr. The reaction mixture was cooled and product isolated as usual and crystallized from acetic acid-water, yield 0.9 g (60%), m.p.220°.

IR(KBr) cm^{-1} : 1700 (CO), 2700-2900 (C-H), 3400 (NH).

NMR(TFA) δ : 1.0 (t, 3H, $CH_2\underline{CH}_3$, J=8Hz), 4.0 (q, 2H, $\underline{CH}_2$ CH_3, J=8Hz), 6.8-7.3 (m, 8H, Ar-H).

Analysis for : $C_{16}H_{15}N_3O_2$ (281)

Calcd. : C, 68.37; H, 5.33

Found : C, 68.56; H, 5.66%.

4-(Benzoyl)amino-3-nitrobiphenyl (128)

A solution of benzoyl chloride (0.77 g, 0.0055 mol) in dry benzene (20 ml) was added dropwise to a refluxing solution of 125 (1.0 g, 0.0046 mol) in dry benzene (30 ml) and refluxing continued for 12 hr. The reaction mixture was cooled and successively washed with water (3x20 ml) and 10% $NaHCO_3$ solution (3x20 ml). The organic layer was dried (Na_2SO_4) and solvent removed *in vacuo* to get a solid mass which was crystallized from benzene, yield 1.2 g (81%), m.p.140°.

IR(KBr) cm^{-1} : 1320, 1580 (NO_2), 1680 (CO).

NMR(DMSO-d_6) δ : 7.25-7.95 (m, 12H, Ar-H), 8.18 (d, 1H, Ar-H, o to NO_2, J=2Hz)

Analysis for : $C_{19}H_{14}N_2O_3$ (318)

Calcd. : C, 71.69; H, 4.46

Found : C, 72.00; H, 4.42%.

Similarly, compounds 129 and 130 were prepared by treating 125 with corresponding acid chlorides in dry benzene.

129, yield 75%, m.p.151°.

IR(KBr) cm^{-1} : 1320, 1520 (NO_2), 1685 (CO).

NMR(DMSO-d_6) δ : 7.32-8.0 (m, 11H, Ar-H), 8.12 (d, 1H, PhC=CH-C-NO_2, J=2Hz)

Analysis for : $C_{19}H_{13}N_3O_5$ (363)

Calcd. : C, 62.90; H, 3.57

Found : C, 63.32; H, 3.83%.

130, yield 76%, m.p.244°.

IR(KBr) cm^{-1} : 1340, 1520 (NO_2), 1680 (CO)

Analysis for : $C_{19}H_{13}N_3O_5$ (363)

Calcd. : C, 62.90; H, 3.57

Found : C, 62.78; H, 3.68%.

3-Amino-4-(benzoyl)aminobiphenyl (131)

To a warm mixture of 128 (1.0 g, 0.0031 mol) and Raney-nickel (~0.2 g) in ethanol-THF (2:1, 50 ml), a solution of hydrazine-hydrate (1.25 g, 0.0248 mol) in ethanol (20 ml) was added dropwise and refluxing continued for 1 hr. Catalyst was filtered off and mother liquor was concentrated to get a solid which was crystallized from ethanol, yield 0.65 g (72%), m.p. 198-200°.

IR(KBr) cm^{-1} : 1635 (CO), 3200-3400 (NH,NH_2).

Analysis for : $C_{19}H_{16}N_2O$ (288)

Calcd. : C, 79.13; H, 5.55

Found : C, 79.43; H, 5.28%.

In similar manner 132 and 133 were prepared by reducing 129 and 130 with hydrazine-hydrate and Raney-nickel in ethanol-THF mixture.

132, yield 64%, m.p.188°.

IR(KBr) cm^{-1} : 1620 (CO), 3200-3300 (NH,NH_2)

Analysis for : $C_{19}H_{17}N_3O$ (303)

Calcd. : C, 75.24; H, 5.61

Found : C, 75.62; H, 5.78%.

133, yield 68%, m.p.228°.

IR(KBr) cm^{-1} : 1625 (CO), 3200-3300 (NH,NH_2)

Analysis for : $C_{19}H_{17}N_3O$ (303)

Calcd. : C, 75.24; H, 5.61

Found : C, 75.38; H, 5.46%.

2,5(6)-Diphenylbenzimidazole (134)

A solution of 131 (1.0 g, 0.0034 mol) in ethanol (10 ml) and concentrated hydrochloric acid (20 ml) was refluxed for 8 hr. The reaction mixture was cooled, the separated solid was filtered and basified with aqueous ammonia solution. The aqueous layer was extracted with ethyl acetate (2x30 ml), dried (Na_2SO_4) and solvent removed *in vacuo* to get pure product, yield 0.58 g (62%), m.p.196° (lit.[42] m.p.197-8°).

IR(KBr) cm^{-1} : 1620 (Arom).

Mass at m/z : 270 (M^+)

Analysis for : $C_{19}H_{14}N_2$

Calcd. : C, 84.10; H, 5.18

Found : C, 83.68; H, 5.53%.

Compounds 135 and 136 were prepared similarly from 132 and 133.

135, yield 63%, m.p.215°.

IR(KBr) cm^{-1} : 1605 (Arom), 3150-3420 (NH,NH_2).

Mass at m/z : 285 (M^+)

Analysis for : $C_{19}H_{15}N_3$ (285)

Calcd. : C, 80.00; H, 5.26

Found : C, 80.32; H, 5.48%.

136, yield 58%, m.p.227-8°.

IR(KBr) cm^{-1} : 1600 (Arom), 3200-3400 (NH,NH_2).

Mass at m/z : 285 (M^+)

Analysis for : $C_{19}H_{15}N_3$ (285)

Calcd. : C, 80.00; H, 5.26

Found : C, 80.24; H, 5.12%.

2-(4-Isothiocyanatophenyl)-5(6)-phenylbenzimidazole-hydrochloride (139)

A solution of thiophosgene (0.27 ml, 0.0035 mol) in dry acetone (10 ml) was added dropwise to a stirred solution of 135 (1.0 g, 0.0035 mol) in dry acetone

(35 ml) at room temperature. The stirring was continued for 8 hr, the separated hydrochloride was filtered, washed with ethyl acetate (3x10 ml) and dried, yield 0.78 g (65%), m.p.295-8°.

IR(KBr) cm^{-1} : 1605 (Arom), 1630 (C=N), 2050 (NCS), 2600-2900 (salt),

Analysis for : $C_{20}H_{13}N_3S.HCl$ (363.5)

Calcd. : C, 66.24; H, 3.85

Found : C, 66.38; H, 3.62%.

2-(4-Carbomethoxyaminophenyl)-5(6)-phenylbenzimidazole(141)

Methyl chloroformate (0.4 g, 0.0042 mol) was added to a solution of 136(1.0 g, 0.0035 mol) in pyridine (20 ml) and the reaction mixture heated at 100° for 1 hr. The reaction mixture was cooled and diluted with water (100 ml). The separated solid was filtered, washed with water, dried and crystallized from ethanol, yield 1.0 g (85%), m.p.210°.

IR(KBr) cm^{-1} : 1600 (Arom), 1710 (CO), 3320 (NH).

NMR(TFA) δ : 3.5 (s, 3H, OCH_3), 6.8-7.6 (m, 12H, Ar-H)

Analysis for : $C_{21}H_{17}N_3O_2$ (343)

Calcd. : C, 73.46; H, 4.95

Found : C, 73.72; H, 5.22%.

Similarly 140 was prepared from 136 and ethyl chloroformate, yield 80%, m.p.255°.

IR(KBr) cm^{-1} : 1600 (Arom), 1700 (CO), 3300-3400 (NH).

NMR(DMSO-d_6) δ : 1.2 (t, 3H, $CH_2\underline{CH}_3$, J=7Hz), 4.1 (q, 2H, $\underline{CH}_2CH_3$, J=7Hz), 7.2-8.3 (m, 12H, Ar-H)

Analysis for : $C_{22}H_{19}N_3O_2$ (357)

Calcd. : C, 73.94; H, 5.32

Found : C, 74.35; H, 5.12%.

9-Phenylbenzimidazo [1,2-c]quinazolin-6-one (137)

A mixture of 135 (1.0 g, 0.0035 mol) and ethyl chloroformate (0.38 g, 0.0035 mol) in pyridine (20 ml) was refluxed for 2 hr. The reaction mixture was cooled and diluted with water. The separated solid was filtered, washed thoroughly with water, dried and crystallized from DMSO, yield 0.83 g (75%), m.p.296°.

IR(KBr) cm^{-1} : 1620 (C=N), 1710 (CO)

Mass at m/z : 311 (M^+)

Analysis for : $C_{20}H_{13}N_3O$ (311)

Calcd. : C, 77.17; H, 4.14

Found : C, 77.38; H, 4.53%.

Under identical reaction condition, 9-phenylbenzimidazo[1,2-c]quinazoline-6-thione (138) was prepared by reaction of 135 with potassium ethyl xanthate in pyridine, yield 72%, m.p.255-6°.

IR(KBr) cm^{-1} : 1160 (C=S), 1630 (C=N).

Mass at m/z : 327 (M^+)

Analysis for : $C_{20}H_{13}N_3S$ (327)

Calcd. : C, 73.39; H, 3.91

Found : C, 73.52; H, 4.26%.

1-(2-Aminobenzoyl)-2-mercapto-5-phenylbenzimidazole (143)

Thiophosgene (0.13 ml, 0.0016 mol) in acetone (20 ml) was added dropwise to a stirred solution of 132 (0.5 g, 0.0016 mol) in dry acetone (30 ml) and triethylamine (0.32 ml, 0.0032 mol) dropwise at room temperature. The stirring was continued for 5 hr and the solid separated was filtered, washed with acetone (3x10 ml), dried and crystallized from DMSO-water, yield 0.24 g (45%), m.p.275°.

IR(KBr) cm^{-1} : 1690 (CO), 3200-3400 (NH_2).

Mass at m/z : 345 (M^+)

Analysis for : $C_{20}H_{15}N_3OS$ (345)

Calcd. : C, 69.56; H, 4.34

Found : C, 70.04; H, 4.15%.

15% of 144 was also obtained from mother liquor.

1-(4-Isothiocyanatobenzoyl)-2-mercapto-5-phenylbenzimidazole (145)

To a stirred solution of 133 (0.5 g, 0.0016 mol) in dry acetone (30 ml) and triethylamine (0.65 ml, 0.0065 mol), a solution of thiophosgene (0.25 ml, 0.0032 mol) in

dry acetone (30 ml) was added dropwise at room temperature. Stirring was continued for 10 hr. Solvent was removed *in vacuo* and the residue crystallized from benzene, yield 0.41 g (65%), m.p.195°.

IR(KBr) cm^{-1} : 1680 (CO), 2060 (NCS).

Mass at m/z : 387 (M^+), base peak 162.

Analysis for : $C_{21}H_{13}N_3OS_2$ (387)

Calcd. : C, 65.11; H, 3.35

Found : C, 65.38; H, 3.25%.

Similarly 144 was prepared from 132 and two moles of thiophosgene and purified by column chromatography using silica gel column and ethyl acetate-benzene (1:4) as eluant, yield 50%, m.p.255-56°.

IR(KBr) cm^{-1} : 1710 (CO), 2080 (NCS)

Mass at m/z : 387 (M^+), base peak 329

Analysis for : $C_{21}H_{13}N_3OS_2$ (387)

Calcd. : C, 65.11; H, 3.35

Found : C, 65.23; H, 3.50%.

5-(4-Acetamidophenylthio)-2-nitroacetanilide (148)

To a solution of 4-acetamidothiophenol (5.0 g, 0.03 mol) in n-propanol (30 ml), 10% aqueous solution of KOH (1.66 g, 0.03 mol) was added at room temperature and stirring was continued for 30 minutes. To this was added a solution of 5-chloro-2-nitroacetanilide 56 (6.42 g, 0.03 mol) in n-propanol (20 ml). The reaction mixture

was refluxed for 5 hr, cooled and the crystallized solid filtered, washed successively with n-propanol (2x10 ml) and water (3x10 ml) and dried, yield 7.8 g (75.5%), m.p.196°.

IR(KBr) cm^{-1} : 1300, 1570 (NO_2), 1600 (Arom), 1660, 1705 (CO), 3280 (NH).

NMR(DMSO-d_6) δ : 2.02 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$ o to NO_2), 6.86 (dd, 1H, Ar-H, p to NHAc, J=3 & 9Hz), 7.4-7.95 (m, 6H, Ar-H), 10.2 (hump, 1H, NHCO).

Analysis for : $C_{16}H_{15}N_3O_4S$ (345)

Calcd. : C, 55.65; H, 4.34

Found : C, 55.95; H, 4.10%.

Similarly 147 was prepared from 4-acetamidothiophenol and 5-chloro-2-nitroaniline (98) in n-propanol.

147 was also prepared by selective hydrolysis of 148 described below.

5-(4-Acetamidophenylthio)-2-nitroaniline (147)

To a suspension of 148 (10.0 g, 0.029 mol) in boiling ethanol (50 ml) was added a solution of KOH (2.0 g) in water (10 ml). The reaction mixture was heated for 5 minutes on a water bath and left at room temperature. The product crystallized after cooling which was filtered, washed with 50% aqueous ethanol and dried, yield 6.2 g

(70.8%), m.p.176-7°.

IR(KBr) cm^{-1} : 1300, 1560 (NO_2), 1600 (Arom), 1650 (CO), 3260, 3340, 3470 (NH,NH_2).

NMR(DMSO-d_6) δ : 2.1 (s, 3H, $COCH_3$), 6.25 (dd, 1H, Ar-H, p to NH_2, J=2&9Hz), 6.55 (d, 1H, Ar-H, o to NH_2, J=2Hz), 7.45 (d, 2H, Ar-H, m to NHAc, J=9Hz), 7.78 (d, 2H, Ar-H, o to NHAc, J=9Hz), 7.84 (d, 1H, Ar-H, o to NO_2, J=9Hz), 10.2 (hump, 1H,NHCO)

Analysis for : $C_{14}H_{13}N_3O_3S$ (303)

Calcd. : C, 55.44; H, 4.29; N, 13.86

Found : C, 55.12; H, 4.65; N, 14.24%.

5-(4-Acetamidophenylthio)-o-phenylenediamine (149)

To a warm mixture of 147 (6.06 g, 0.02 mol) and Raney-nickel (~ 0.8 g) in ethanol-THF (1:1, 50 ml), was added dropwise hydrazine-hydrate in ethanol (8.0 g, 0.16 mol) with occassional shaking. When solution became colourless the catalyst was filtered off, washed with ethanol (3x10 ml) and the filtrate was evaporated in vacuo to get crude diamine, yield 3.8 g (78.1%). This product was as such used in next step.

Ethyl 5(6)-(4-acetamidophenylthio)benzimidazole-2-carbamate (151)

A mixture of 149 (9.0 g, 0.033 mol) and 1,3-dicarbethoxy-S-methylisothiourea (7.7 g, 0.0034 mol) in ethanol

(150 ml) was refluxed for 16 hr. The reaction mixture was cooled and the separated solid was filtered, washed with ethanol, dried and recrystallized from acetic acid-water, yield 8.69 g (70.4%), m.p.235-6°.

IR(KBr) cm^{-1} : 1650 ($COCH_3$), 1700 (NHCOO), 2700-2800 (C-H), 3400 (NH).

NMR(TFA) δ : 0.98 (t, 3H, $CH_2\underline{CH}_3$, J=8Hz), 2.0 (s, 3H, $CO\underline{CH}_3$), 3.98 (q, 2H, $\underline{CH}_2CH_3$, J=8Hz), 6.8-7.1 (m, 7H, Ar-H)

Analysis for : $C_{18}H_{18}N_4O_3S$ (370)

Calcd. : C, 58.37; H, 4.86; N, 15.13

Found : C, 58.68; H, 4.44; N, 15.46%.

Using similar experimental condition 150 was also prepared from 149 and 1,3-dicarbomethoxy-S-methylisothiourea in refluxing ethanol.

5(6)-(4-Acetamidophenylthio)-2-methylbenzimidazole (153)

A solution of 149 (7.5 g, 0.027 mol) in glacial acetic acid (40 ml) was refluxed overnight. The reaction mixture was cooled and the crystallized salt of the product was filtered, washed with benzene and treated with aqueous ammonia to give free base (3.7 g). Another crop of pure product (2.8 g) was obtained from the mother liquor on neutralization with 30% aqueous ammonia solution, total yield 6.5 g (79.7%), m.p.258-60°.

IR(KBr) cm^{-1} : 1680 (CO), 3250 (NH).

NMR(TFA) δ : 2.08 (s, 3H, $COC\underline{H}_3$), 2.49 (s, 3H, $C-C\underline{H}_3$), 6.9-7.25 (m, 7H, Ar-H)

Analysis for : $C_{16}H_{15}N_3OS$ (297)

Calcd. : C, 64.64; H, 5.05

Found : C, 64.26; H, 5.44%.

Compound 152 was prepared similarly from 149 and formic acid.

5(6)-(4-Acetamidophenylsulfono)-2-methylbenzimidazole (162)

$KMnO_4$ (4.0 g) was added to a stirred solution of 153 (4.0 g, 0.013 mol) in 80% aqueous acetic acid (250 ml) during 30 minutes at room temperature. Stirring was continued for further 5 hr and then excess of $KMnO_4$ was decomposed by careful addition of 30% H_2O_2 solution during cooling. When the reaction mixture became colourless, it was diluted with large amount of water. The solid separated after 30 minutes was filtered, washed with water and dried to get pure compound, yield 3.4 g (77.2%), m.p. $>280^{\circ}$.

IR(KBr) cm^{-1} : 1155 (SO_2), 1690 (CO), 3200-3400 (NH),

NMR(DMSO-d_6) δ : 2.03 (s, 3H, $COC\underline{H}_3$), 2.48 (s, 3H, $C-C\underline{H}_3$), 7.5-7.9 (m, 7H, Ar-H)

Analysis for : $C_{16}H_{15}N_3O_3S$ (329)

Calcd. : C, 58.35; H, 4.55

Found : C, 58.72; H, 4.92%

Similarly compounds 159-161 were prepared by oxidation of 150-152 respectively.

5(6)-(4-Aminophenylsulfono)-2-methylbenzimidazole (167)

A solution of 162 (1.0 g, 0.003 mol) in concentrated HCl (20 ml) was refluxed for 12 hr. The reaction mixture was cooled, and the separated hydrochloride filtered, washed with benzene (3x10 ml), dried and neutralized with 30% aqueous ammonia solution to get a pure free base, yield 0.65 g (74.7%), m.p.130°.

IR(KBr) cm^{-1} : 1140 (SO_2), 3100-3400 (NH,NH_2).

NMR(DMSO-d_6) δ : 2.48 (s, 3H, C-CH_3), 5.96 (s, 2H, NH_2), 6.53 (d, 2H, Ar-H, o to NH_2, J=9Hz), 7.35-7.95 (m, 5H, Ar-H)

Analysis for : $C_{14}H_{13}N_3O_2S$ (287)

Calcd. : C, 58.53; H, 4.52

Found : C, 58.22; H, 4.12%.

Similarly 156, 157 and 166 were obtained by hydrolysis of 152, 153 and 161 with concentrated HCl.

Ethyl 5(6)-(4-aminophenylsulfono)benzimidazole-2-carbamate (164)

A solution of 160 (1.0 g, 0.0025 mol) in 10% HCl (50 ml) was heated on water bath for 30 minutes. The reaction mixture was cooled in ice and neutralized with 30% aqueous ammonia solution. The separated solid was filtered,

washed with water and dried. It was purified by acid-base treatment, yield 0.76 g (85.3%), m.p.250°.

IR(KBr) cm^{-1} : 1140 (SO_2), 1715 (NHCOO), 2750-2950 (C-H), 3100-3350 (NH,NH_2).

NMR(TFA) δ : 0.98 (t, 3H, $CH_2\underline{CH}_3$, J=7Hz), 4.0 (q, 2H, $\underline{CH}_2$-CH_3, J=7Hz), 7.1-8.9 (m, 7H, Ar-H)

Analysis for : $C_{16}H_{16}N_4O_4S$ (360)

Calcd. : C, 53.33; H, 4.44

Found : C, 53.74; H, 4.82%.

Similarly 154, 155 and 163 were prepared from 150, 151 and 159 respectively in 10% HCl.

When 150, 151, 159 and 160 were refluxed in concentrated HCl for 24-30 hr complete hydrolysis took place giving rise to compounds 158 and 165 respectively.

5(6)-(4-Isothiocyanatophenylsulfono)-2-methylbenzimidazole (175)

Thiophosgene (0.14 ml, 0.0018 mol) in acetone (15 ml) was added dropwise to a stirred solution of 167 (0.5 g, 0.0017 mol) in acetone (120 ml) at room temperature. The stirring was continued for 6 hr. The solvent was removed in vacuo and the solid obtained was washed with water (3x10 ml) and hexane (3x10 ml) to get 175, yield 0.38 g (66.6%), m.p.220-22°.

IR(KBr) cm^{-1} : 1150 (SO_2), 2050 (NCS).

NMR(TFA) δ : 2.56 (s, 3H, C-CH_3), 6.9-8.1 (m, 7H, Ar-H)

Analysis for : $C_{15}H_{11}N_3O_2S_2$ (329)

Calcd. : C, 54.71; H, 3.34

Found : C, 54.84; H, 3.08%.

Similarly compounds 168-174 were prepared from 154, 155, 157, 158, 163, 164 and 166 in large amount of acetone due to their poor solubility.

5-(4-Acetamidophenoxy)-2-nitroaniline (176)

A solution of potassium 4-acetamidophenoxide 94 (15.0 g, 0.079 mol) and 5-chloro-2-nitroaniline 98 (13.7 g, 0.0079 mol) in dry DMF (50 ml) was refluxed for 24 hr. The reaction mixture was cooled, diluted with water (250 ml) and extracted with ethyl acetate (3x50 ml). The combined extracts were dried (Na_2SO_4) and solvent was removed in vacuo. The residue was crystallized from aqueous ethanol to get 8.2 g product. The filtrate was chromatographed over silica gel column using benzene and 20% ethyl acetate-benzene as eluant to get 1.8 g more product and starting material, total yield 10.0 g (44%), m.p.218°.

IR(KBr) cm^{-1} : 1360, 1510 (NO_2), 1620 (Arom), 1680 (CO), 3330, 3460 (NH, NH_2).

NMR($CDCl_3$ + DMSO-d_6) δ : 2.03 (s, 3H, $COCH_3$), 6.02-6.2 (m, 2H, Ar-H, o and p to NH_2), 6.86 (d, 2H,

Ar-H, m to NHAc, J=9Hz), 7.07 (s, 2H, NH_2), 7.52 (d, 2H, Ar-H, o to NHAc, J=9Hz), 7.85 (d, 1H, Ar-H, o to NO_2, J=9Hz), 9.59 (s, 1H, NH)

Analysis for : $C_{14}H_{13}N_3O_4$ (287)

Calcd. : C, 58.53; H, 4.52

Found : C, 58.21; H, 4.62%.

4-(4-Acetamidophenoxy)-o-phenylenediamine (177)

To a warm solution of 176 (10.0 g, 0.034 mol) in ethanol-THF (1:1, 100 ml) and Raney-nickel (1.5 g) was added dropwise with stirring a solution of hydrazine-hydrate (14 g, 0.28 mol) in ethanol (20 ml). The stirring and heating was continued for few minutes and the product isolated as usual, yield 6.8 g (76%). This was not purified and used in further reactions.

Methyl 5(6)-(4-acetamidophenoxy)benzimidazole-2-carbamate (178)

A mixture of 177 (2.0 g, 0.0076 mol) and 1,3-dicarbomethoxy-S-methylisothiourea (1.68 g, 0.008 mol) in ethanol (50 ml) was refluxed for 15 hr. The reaction mixture was worked-up in usual manner and the product recrystallised from acetic acid-water, yield 2.2 g (83.3%), m.p. $>280^{o}$.

IR(KBr) cm^{-1} : 1600 (Arom.), 1670, 1710 (CO), 2700-2800 (C-H), 3310 (NH).

NMR(TFA) δ : 2.07 (s, 3H, $COCH_3$), 3.57 (s, 3H, OCH_3), 6.6-7.2 (m, 7H, Ar-H)

Analysis for : $C_{17}H_{16}N_4O_4$ (340)

Calcd. : C, 60.00; H, 4.70

Found : C, 60.42; H, 4.25%.

In similar manner compound 179 was prepared from 177 and 1,3-dicarbethoxy-S-methylisothiourea in refluxing ethanol.

Methyl 5(6)-(4-aminophenoxy)benzimidazole-2-carbamate (180)

A solution of 178 (0.5 g, 0.0014 mol) in 10% HCl (50 ml) was heated on water bath for 30 minutes. The reaction mixture was cooled, neutralized with aqueous ammonia solution. The solid thus separated was filtered, washed with water (3x10 ml) and dried, yield 0.36 g (83.7%), m.p.285°.

IR(KBr) cm^{-1} : 1600 (Arom), 1720 (CO), 2650-2800 (C-H), 3250-3320 (NH,NH_2)

NMR(TFA) δ : 3.58 (s, 3H, OCH_3), 6.7-7.2 (m, 7H, Ar-H)

Analysis for : $C_{15}H_{14}N_4O_3$ (298)

Calcd. : C, 60.40; H, 4.69

Found : C, 60.72; H, 4.24%.

In similar way 181 was prepared by hydrolysing 179 in 10% HCl for 30 minutes.

5(6)-(4-Acetamidophenoxy)benzimidazole (182)

A solution of 177 (1.0 g, 0.0038 mol) in 98% formic acid was heated for 2 hr on a water bath. The reaction mixture was cooled and neutralized with aqueous ammonia solution. The separated solid was filtered, washed with water, dried and purified by acid base treatment, yield 0.55 g (63.1%), m.p.80-2°.

IR(KBr) cm^{-1} : 1640 (CO), 3100-3200 (NH).

NMR(DMSO-d_6) δ : 2.02 (s, 3H, $COCH_3$), 6.76-7.6 (m, 7H, Ar-H), 8.13 (s, 1H, N=CH-N)

Analysis for : $C_{15}H_{13}N_3O_2$ (267)

Calcd. : C, 67.41; H, 4.86

Found : C, 67.15; H, 5.28%.

Compound 183 was prepared similarly from 177 and glacial acetic acid.

5(6)-(4-Aminophenoxy)benzimidazole dihydrochloride (184)

182 (0.5 g, 0.0018 mol) in concentrated HCl (20 ml) was refluxed for 4 hr. The reaction mixture was cooled and the separated hydrochloride was filtered, washed with dry ether and dried, yield 0.4 g (71.4%), m.p.240-2°.

IR(KBr) cm^{-1}(HCl): 1600 (Arom), 2500-2850 (salt).

NMR(D_2O)(HCl) δ : 7.15-7.9 (m, 7H, Ar-H), 9.22 (s, 1H, N=CH-N)

Analysis for : $C_{13}H_{13}Cl_2N_3O$ (298)

Calcd. : C, 52.34; H, 4.36

Found : C, 52.68; H, 4.86%.

Similarly 185 was prepared by hydrolysis of 183 in concentrated HCl.

Methyl 5(6)-(4-isothiocyanatophenoxy)benzimidazole-2-carbamate (186)

A solution of thiophosgene (0.13 ml, 0.0016 mol) in acetone (20 ml) was added dropwise to a stirred solution of 180 (0.5 g, 0.0016 mol) in acetone (100 ml) at room temperature. Stirring was continued for 5 hr at same temperature and then the solvent removed in vacuo. The product was precipitated while washing with water. The solid thus obtained, was purified by filtration through silica gel column using chloroform as eluant, yield 0.46 g (80.7%), m.p.220°.

IR(KBr) cm^{-1} : 1720 (CO), 2100 (NCS), 3380 (NH).

NMR(TFA) δ : 3.6 (s, 3H, OCH_3), 6.6-7.3 (m, 7H, Ar-H)

Analysis for : $C_{16}H_{12}N_4O_3S$ (340)

Calcd. : C, 56.47; H, 3.52

Found : C, 56.82; H, 3.12%.

Similarly 187-189 were prepared by treating thiophosgene with their respective amines 181, 184 and 185.

4-Chloro-3-nitrobenzaldehyde (190)

4-Chlorobenzaldehyde (50 g, 0.35 mol) was added gradually to a stirred mixture of KNO_3 (27.5 g) in H_2SO_4 (300 ml) at 15-20°. The mixture was heated at 70° for 30 minutes. The reaction mixture was cooled and poured on ice. The solid, thus obtained, was filtered, washed with water, dried and recrystallized from chloroform-hexane, yield 26.4 g (40%), m.p.64° (lit.[47] m.p.64.5-65°).

4-Chloro-3-nitrobenzyl alcohol (191)

Sodium borohydride (2.24 g) was added in small portions to an ice cooled, stirred solution of 190 (24.0 g, 0.128 mol) in methanol (100 ml). The reaction mixture was stirred for 3 hr and solvent removed in vacuo. The residue was taken in benzene (100 ml) and washed with water (5x20 ml), dried (Na_2SO_4) and concentrated. The resulting solid was recrystallized from chloroform-hexane, yield 14.0 g (57.8%), m.p.64° (lit.[48] m.p.64-65°).

4-Amino-3-nitrobenzyl alcohol (192)

A mixture of 191 (1.0 g, 0.0053 mol), ethanol (10 ml) and aqueous ammonia (20 ml, d=0.88) was heated in steel bomb at 140-50° for 20 hr. The reaction mixture was cooled, solvent removed in vacuo and extracted with ethyl acetate (3x20 ml). The combined extracts were dried (Na_2SO_4), concentrated and the crude product was purified by column chromatography using silica gel column and chloroform as eluant, yield 0.58 g (65.1%), m.p.108°.

IR(KBr) cm^{-1} : 1340, 1520 (NO_2), 3320, 3450 (NH_2,OH).

Mass at m/z : 168 (M^+)

NMR(DMSO-d_6) δ : 4.32 (s, 2H, $C\underline{H}_2OH$), 6.9 (d, 1H, Ar-H, o to NH_2, J=9Hz), 7.2-7.32 (m, 3H, Ar-H and $N\underline{H}_2$), 7.82 (d, 1H, Ar-H, o to NO_2, J=2Hz)

Analysis for : $C_7H_8N_2O_3$ (168)

Calcd. : C, 50.0; H, 4.76; N, 16.66

Found : C, 49.52; H,4.95; N, 16.24%.

4-Chloro-3-nitrobenzyl bromide (194)

To a stirred and cooled solution of 191 (25.0 g, 0.13 mol) in dry benzene (350 ml) was added dropwise PBr_3 (14.4 ml) in dry benzene (80 ml). Stirring was continued for 4-5 hr at room temperature. The reaction mixture was

poured in 500 ml cold water. The benzene layer was separated, washed with water, dried (Na_2SO_4) and concentrated to get an oil, which was purified using silica gel column and hexane as eluant, yield 30 g (89%).

IR(neat) cm^{-1} : 1350, 1540 (NO_2).

NMR($CDCl_3$) δ : 4.35 (s, 2H, $C\underline{H}_2Br$), 7.38 (s, 2H, Ar-H, m and p to NO_2), 7.75 (d, 1H, Ar-H, o to NO_2, J=2Hz)

Analysis for : $C_7H_5BrClNO_2$ (250.5)

Calcd. : C, 33.53; H, 1.99

Found : C, 33.14; H, 2.41%.

2-Nitro-4-phenoxymethylchlorobenzene (195)

A mixture of 194 (10.0 g, 0.039 mol), phenol (3.8 g, 0.04 mol) and K_2CO_3 (6.5 g) in dry acetone (200 ml) was refluxed with constant stirring for 16 hr. The reaction mixture was cooled, solvent was removed in vacuo and the residue taken in benzene. The solution was washed successively with water, 10% NaOH solution and water, dried (Na_2SO_4) and concentrated to get an oil which was chromatographed over silica gel column in hexane, yield 8.8 g (83.5%),

IR(neat) cm^{-1} : 1360, 1540 (NO_2), 1605 (Arom).

NMR($CDCl_3$) δ : 4.96 (s, 2H, $OC\underline{H}_2$), 6.75-7.45 (m, 7H, Ar-$\underline{H}$, $OC_6\underline{H}_5$ and $\underline{m}$ and $\underline{p}$ to NO_2), 7.8 (d, 1H, Ar-$\underline{H}$, $\underline{o}$ to NO_2, J=2Hz)

Analysis for : $C_{13}H_{10}NO_3Cl$ (263.5)

Calcd. : C, 59.20; H, 3.79

Found : C, 58.78; H, 3.38%.

Similarly, 196 was prepared from 194 and thiophenol, as an oil, yield 85%.

IR(neat) cm^{-1} : 1340, 1540 (NO_2).

Mass at m/z : 279 and 281 (M^+)

NMR(CCl_4) δ : 3.94 (s, 2H, S-$C\underline{H}_2$), 7.12 (s, 5H, $SC_6\underline{H}_5$), 7.25 (s, 2H, Ar-$\underline{H}$, $\underline{m}$ and $\underline{p}$ to NO_2), 7.52 (d, 1H, Ar-$\underline{H}$, $\underline{o}$ to NO_2 J=2Hz)

Analysis for : $C_{13}H_{10}ClNO_2S$ (279.5)

Calcd. : C, 55.81; H, 3.57

Found : C, 56.25; H, 3.22%.

2-Thiophenoxy-5-thiophenoxymethylnitrobenzene (197)

Reaction of 194 with 2 moles of thiophenol in presence of KOH in refluxing ethanol yielded the product which was purified by column chromatography using silica gel column and hexane as eluant, yield 68%, m.p.86-7°.

IR(KBr) cm^{-1} : 1340, 1520 (NO_2).

Mass at m/z : 353 (M^+)

NMR($CDCl_3$) δ : 3.92 (s, 2H, S-C<u>H</u>$_2$), 6.62 (d, 1H, Ar-<u>H</u>, <u>m</u> to NO_2, J=9Hz), 7.13 (s, 6H, Ar-<u>H</u>, $CH_2SC_6\underline{H}_5$ and <u>p</u> to NO_2), 7.36 (s, 5H, $SC_6\underline{H}_5$), 7.95 (d, 1H, Ar-<u>H</u>, <u>o</u> to NO_2, J=2.5 Hz)

Analysis for : $C_{19}H_{15}NO_2S_2$ (353)

Calcd. : C, 64.58; H, 4.24; N, 3.96

Found : C, 64.42; H, 4.54; N, 4.42%.

2-Nitro-4-phenoxymethylaniline (<u>198</u>)

A mixture of <u>195</u> (1.0 g, 0.0037 mol), aqueous ammonia solution (20 ml, d=0.88) and ethanol (20 ml) was heated in steel bomb for 20 hr at 150°. The solvent was removed <u>in vacuo</u> and residue extracted with ethyl acetate (3x30 ml). The combined extracts were dried (Na_2SO_4) and concentrated. The product was purified on silica gel column using hexane-benzene (1:1) as eluant, yield 0.35 g (38%), m.p.112°.

IR(KBr) cm^{-1} : 1340, 1560 (NO_2), 3310, 3450 (NH_2).

Mass at m/z : 244 (M^+)

NMR(DMSO-d_6) δ : 4.89 (s, 2H, OC<u>H</u>$_2$), 6.84-7.37 (m, 9H, Ar-<u>H</u> & N<u>H</u>$_2$), 7.97 (d, 1H, Ar-<u>H</u>, <u>o</u> to NO_2, J=2.5Hz)

Analysis for : $C_{13}H_{12}N_2O_3$ (244)

Calcd. : C, 63.93; H, 4.91; N, 11.67

Found : C, 64.35; H, 5.26; N, 11.42%.

Similarly 199 was prepared from 197 and NH_3 in THF-aqueous ammonia in steel bomb at 150°.

Yield (37.7%), m.p.84-5°.

IR(KBr) cm^{-1} : 1340, 1560 (NO_2), 3340, 3480 (NH_2).

Mass at m/z : 260 (M^+)

NMR(DMSO-d_6) δ : 4.06 (s, 2H, S-CH_2), 6.87 (d, 1H, Ar-H, o to NH_2, J=9Hz), 7.1-7.4 (m, 8H, Ar-H & NH_2), 7.81 (d, 1H, Ar-H, o to NO_2, J=2.5Hz).

Analysis for : $C_{13}H_{12}N_2O_2S$ (260)

Calcd. : C, 63.92; H, 4.91; N, 11.47

Found : C, 64.12; H, 5.28; N, 11.20%.

4-Thiophenoxymethyl-o-phenylenediamine (200)

A hot solution of $FeSO_4$ (4.0 g) in aqueous ammonia (25 ml) was added to a hot solution of 199 (0.5 g, 0.002 mol) in acetone (20 ml) and aqueous ammonia solution (25 ml). The reaction mixture was heated for 30 minutes on water bath and the product worked-up as usual, yield 0.35 g (79.5%). This product was used as such in further steps.

Methyl 5(6)-thiophenoxymethylbenzimidazole-2-carbamate (201)

A mixture of 200 (0.35 g, 0.0015 mol) and 1,3-dicarbomethoxy-S-methylisothiourea (0.5 g, 0.002 mol) in ethanol (25 ml) was refluxed for 15 hr. Usual work-up of

the reaction mixture gave the product which was recrystallized from ethanol or acetic acid-water, yield 0.4 g (85%), m.p.200°.

IR(KBr) cm^{-1} : 1600 (Arom) 1710 (CO), 3300 (NH).

Mass at m/z : 313 (M^+)

NMR(TFA) δ : 3.54 (s, 3H, $OC\underline{H}_3$), 3.71 (s, 2H, $SC\underline{H}_2$), 6.73 (s, 5H, Ar-$\underline{H}$, S-$C_6\underline{H}_5$), 6.95 (d, 3H, Ar-$\underline{H}$ benzimidazole)

Analysis for : $C_{16}H_{15}N_3O_2S$ (313)

Calcd. : C, 61.34; H, 4.79; N, 13.41

Found : C, 61.52; H, 4.58; N, 13.28%

Similarly, compound 202 was prepared from 200 and 1,3-dicarbethoxy-S-methylisothiourea, yield 75%, m.p. 250°.

IR(KBr) cm^{-1} : 1600 (Arom), 1700 (CO), 2700-2900 (C-H), 3300 (NH).

Mass at m/z : 327 (M^+)

Analysis for : $C_{17}H_{17}N_3O_2S$ (327)

Calcd. : C, 62.38; H, 5.19; N, 12.84

Found : C, 62.80; H, 5.56; N, 13.12%.

1,2-Di-(4-acetamidophenylthio)ethane (203)

A mixture of 4-acetamidothiophenol (94 5.0 g, 0.03 mol) and KOH (1.67 g, 0.03 mol) in ethanol (50 ml) was stirred at room temperature for 30 minutes. To this

solution was added, a solution of dibromoethane (1.3 ml, 0.014 mol) in ethanol (10 ml) dropwise with stirring. Stirring was continued and reaction mixture heated for 30 minutes. The separated solid was filtered off, washed with ethanol (3x10 ml), water (3x10 ml) and dried, yield 4.5 g (84.8%), m.p.268°.

IR(KBr) cm^{-1} : 1600 (Arom), 1670 (CO), 3300 (NH).

NMR(DMSO-d_6) δ : 2.02 (s, 6H, 2x$COC\underline{H}_3$), 2.98 (s, 4H, $S(C\underline{H}_2)_2S$), 7.15 (d, 4H, Ar-$\underline{H}$, $\underline{o}$ to S, J=9Hz), 7.50 (d, 4H, Ar-$\underline{H}$, $\underline{o}$ to NHAc, J=9Hz), 10.0 (s, 2H, 2x$N\underline{H}$, D_2O exchangeable)

Analysis for : $C_{18}H_{20}N_2O_2S_2$ (360)

Calcd. : C, 60.00; H, 5.55; N, 7.77

Found : C, 60.38; H, 5.88; N, 8.12%.

Similarly 204 was prepared from 94 and 1,3-dibromopropane in presence of KOH in ethanol and purified by filtration through silica gel column using benzene as eluant, yield 80%, m.p.120-21°.

IR(KBr) cm^{-1} : 1600 (Arom), 1660 (CO), 3300 (NH).

NMR($CDCl_3$ + DMSO-d_6) δ : 1.77 (t, 2H, C-$C\underline{H}_2$-C, J=6Hz), 2.02 (s, 6H, 2x$COC\underline{H}_3$), 2.87 (t, 4H, $S(C\underline{H}_2)_2$, J=6Hz), 7.13 (d, 4H, Ar-$\underline{H}$, $\underline{m}$ to NHAc, J=9Hz), 7.42 (d, 4H, Ar-$\underline{H}$, $\underline{o}$ to NHAc, J=9Hz), 9.4 (s, 2H, 2x$N\underline{H}CO$)

Analysis for : $C_{19}H_{22}N_2O_2S_2$ (374)

Calcd. : C, 69.62; H, 5.88

Found : C, 70.04; H, 6.28%.

1,2-Di-(4-acetamidophenylsulfono)ethane (205)

To a suspension of 203 (5.0 g, 0.013 mol) in acetic acid-water (8:2, 250 ml), $KMnO_4$ (10 g) was added in three portions at 30 minutes interval with stirring at room temperature. The stirring was continued for 4 hr. The reaction mixture was cooled, the excess $KMnO_4$ was decomposed using H_2O_2 solution. It was diluted with water (500 ml). The separated pure solid was filtered, washed with water several times and dried, yield 4.2 g (71.18%), m.p.282°.

IR(KBr) cm^{-1} : 1160 (SO_2), 1600 (Arom), 1680 (CO), 3300 (NH).

NMR(DMSO-d_6) δ : 2.03 (s, 6H, 2x$COCH_3$), 3.4 (s, 4H, $SO_2(CH_2)_2SO_2$), 7.67 (s, 8H, Ar-H).

Analysis for : $C_{18}H_{20}N_2O_6S_2$ (424)

Calcd. : C, 50.46; H, 4.67; N, 6.54

Found : C, 50.86; H, 4.25; N, 6.80%.

Similarly 206 was prepared by oxidizing 204 with $KMnO_4$ in 80% aqueous acetic acid.

Yield 64.5%, m.p.238°.

IR(KBr) cm^{-1} : 1140 (SO_2), 1590 (Arom), 1690 (CO), 3250 (NH).

Mass at m/z : 438 (M^+)

NMR($CDCl_3$ + $DMSO-d_6$) δ : 1.7-1.9 (m, 2H, C-CH_2), 2.1 (s, 6H, 2x$COCH_3$), 3.14 (t, 4H, 2xSO_2CH_2, J=6Hz), 7.55 (d, 4H, Ar-H, m to NHAc, J=9Hz), 7.78 (d, 4H, Ar-H, o to NHAc, J=9Hz), 10.05 (s, 2H, 2xNHCO)

Analysis for : $C_{19}H_{22}N_2O_6S_2$ (438)

Calcd. : C, 52.05; H, 5.02

Found : C, 52.48; H, 5.36%.

1,2-Di-(4-aminophenylthio)ethane (207)

A solution of 203 (0.5 g, 0.0013 mol) in concentrated HCl (25 ml) was refluxed overnight. The reaction mixture was cooled, neutralized with aqueous ammonia solution. The separated amine was filtered, washed with water and dried, yield 0.25 g (65.7%), m.p.100°.

IR(KBr) cm^{-1} : 1600 (Arom), 3320-3430 (NH_2).

NMR($CDCl_3$ + $DMSO-d_6$) δ : 2.7 (s, 4H, $S(CH_2)_2S$), 4.55 (bs, 4H, 2xNH_2), 6.42 (d, 4H, Ar-H, o to NH_2, J=9Hz), 6.94 (d, 4H, Ar-H, m to NH_2, J=9Hz).

Analysis for : $C_{14}H_{16}N_2S_2$ (276)

Calcd. : C, 60.43; H, 5.75; N, 10.71

Found : C, 60.82; H, 5.32; N, 10.38%.

Similarly 208 and 209 were prepared from 205 and 206

by refluxing it with concentrated HCl.

208, yield 72%, m.p. >300°.

IR(KBr) cm^{-1} : 1160 (SO_2), 3380, 3480 (NH_2).

NMR(DMSO-d_6) δ : 3.21 (s, 4H, $SO_2(CH_2)_2SO_2$), 6.15 (s, 4H, 2xNH_2), 6.56 (d, 4H, Ar-H, o to NH_2, J=9Hz), 7.36 (d, 4H, Ar-H, m to NH_2, J=9Hz)

Analysis for : $C_{14}H_{16}N_2O_4S_2$ (340)

Calcd. : C, 49.41; H, 4.70; N, 8.23

Found : C, 49.80; H, 5.20; N, 8.58%.

209 (2HCl), yield 70%, m.p.255°.

IR(KBr) cm^{-1} : 1150 (SO_2), 2550-2820 (Salt).

NMR(TFA) δ : 1.7-2.2 (m, 2H, C-CH_2-C), 2.9-3.4 (m, 4H, 2xSO_2CH_2), 7.3-7.9 (m, 8H, Ar-H)

1,2-Di-(4-isothiocyanatophenylthio)ethane (210)

Thiophosgene (0.22 ml, 0.0028 mol) was added to a stirred solution of 207 dihydrochloride (0.5 g, 0.0014 mol) in 50% aqueous acetic acid. The stirring was continued for 3 hr at room temperature. The separated solid was filtered, washed with water and dried, yield 0.28 g (55%), m.p. 280°.

IR(KBr) cm^{-1} : 2100 (NCS).

Mass at m/z : 360 (M^+)

Analysis for : $C_{16}H_{12}N_2S_4$ (360)

Calcd. : C, 53.33; H, 3.33

Found : C, 53.68; H, 3.22%.

Similarly 211 and 212 were prepared from 208 and 209 and thiophosgene in 50% aqueous acetic acid and 10% HCl respectively.

211, yield 62%, m.p. $>280^{\circ}$.

IR(KBr) cm^{-1} : 1140 (SO_2), 1580 (Arom), 2100 (NCS).

Mass at m/z : 424 (M^+)

Analysis for : $C_{16}H_{12}N_2O_4S_4$ (424)

Calcd. : C, 45.28; H, 3.77

Found : C, 45.58; H, 3.56%.

212, yield 55%, m.p.178-80°.

IR(KBr) cm^{-1} : 1140 (SO_2), 1590 (Arom), 2100 (NCS).

Mass at m/z : 438 (M^+)

Analysis for : $C_{17}H_{14}N_2O_4S_4$ (438)

Calcd. : C, 46.57; H, 3.19

Found : C, 46.68; H, 3.48%.

General Method for preparing aryl isothiocyanates (219-223)

Various aryl isothiocyanates (219-223) were prepared by the method as described for 2-chloro-4-nitrophenyl

isothiocyanate (220) from their respectively amines (214-218).

Thiophosgene (8.9 ml, 0.116 mol) in acetone (50 ml) was added dropwise to a stirred solution of 215 (20 g, 0.1158 mol) in acetone (250 ml) during 30 minutes at room temperature. The stirring was continued for 3-4 hr, solvent was removed *in vacuo* and the resulting solid was crystallized from hexane, yield 20.5 g (85.6%), m.p.102-4°.

IR(KBr) cm^{-1} : 1340, 1530 (NO_2), 2040 (NCS).

NMR($CDCl_3$) δ : 7.25 (d, 1H, Ar-H, m to NO_2, J=8.5Hz), 8.02 (dd, 1H, Ar-H, p to chloro, J=3 & 8.5Hz), 8.17 (d, 1H, Ar-H, o to chloro, J=3Hz).

Analysis for : $C_7H_3ClN_2O_2S$ (214.5)

Calcd. : C, 39.42; H, 1.74

Found : C, 39.10; H, 1.40%.

N-(4-Isothiocyanatophenyl)-1-methyl-4-piperazinylthiocarboxamide (224)

A solution of N-methylpiperazine (0.57 ml, 0.0052 mol) in acetone (100 ml) was added dropwise to a stirred solution of 223 (1.0 g, 0.0052 mol) in acetone (300 ml) during 1 hr. Stirring was continued for 4 hr at room temperature. The solvent was removed from the reaction mixture and the solid thus obtained was

recrystallized from chloroform, yield 1.2 g (79.8%), m.p.190-3°.

IR(KBr) cm^{-1} : 2070 (NCS), 2800, 2900 (C-H), 3150 (NH).

NMR(DMSO-d_6) δ : 2.31 (s, 3H, N-C<u>H</u>$_3$), 2.51 (t, 4H, N(C<u>H</u>$_2$)$_2$, J=5Hz), 3.55-3.75 (hump, 1H, N<u>H</u>), 3.97 (t, 4H, CSN(C<u>H</u>$_2$)$_2$, J=5Hz), 7.12-7.34 (m, 4H, Ar-<u>H</u>)

Analysis for : $C_{13}H_{16}N_4S_2$ (292)

Calcd. : C, 53.42; H, 5.47

Found : C, 53.76; H, 5.28%.

Similarly compounds <u>225</u> and <u>226</u> were prepared by reaction of <u>223</u> with corresponding piperazines.

N-(4-Nitrophenyl)-1-methyl-4-piperazinylthiocarboxamide (<u>227</u>)

A solution of N-methylpiperazine (5 ml, 0.045 mol) in benzene (20 ml) was added dropwise to a stirred solution of <u>219</u> (8.0 g, 0.044 mol) in benzene (50 ml) at room temperature. Stirring was continued for 3 hr, the product isolated as above and crystallized from chloroform-hexane, yield 10.2 g (81.6%), m.p.100-102°.

IR(KBr) cm^{-1} : 1325, 1540 (NO_2), 2800, 2900 (C-H), 3150 (NH).

NMR($CDCl_3$ + DMSO-d_6) δ : 2.33 (s, 3H, N-C<u>H</u>$_3$), 2.50 (t, 4H, N(C<u>H</u>$_2$)$_2$, J=5Hz), 2.7-2.93 (hump, 1H, N<u>H</u>),

4.00 (t, 4H, $CSN(C\underline{H}_2)_2$, J=5Hz), 8.00 (d, 2H, Ar-$\underline{H}$, $\underline{m}$ to NO_2, J=9Hz), 8.10 (d, 2H, Ar-$\underline{H}$, $\underline{o}$ to NO_2, J=9Hz).

Analysis for : $C_{12}H_{16}N_4O_2S$ (280)

Calcd. : C, 51.42; H, 5.71

Found : C, 51.14; H, 5.36%.

In similar manner compounds 228-235 were prepared by treating 219-221 with the corresponding piperazines.

N-(4-Acetylaminophenyl)-1-methyl-4-piperazinylthiocarboxamide (236)

A solution of N-methylpiperazine (0.57 ml, 0.0052 mol) in acetone (50 ml) was added dropwise to a stirred solution of 222 (1.0 g, 0.0052 mol) and the reaction mixture was refluxed for 3 hr. The separated solid was filtered and recrystallized from acetone, yield 1.1 g (72.5%), m.p.212°.

IR(KBr) cm^{-1} : 1670 (CO), 2700-2800 (C-H), 3200 (NH).

NMR($CDCl_3$ + DMSO-d_6) δ : 2.02 (s, 3H, $CO\underline{CH}_3$), 2.23 (s, 3H, N-$\underline{CH}_3$), 2.34-2.5 (m, 4H, CH_3-$N(C\underline{H}_2)_2$), 3.83 (t, 4H, $CSN(C\underline{H}_2)_2$, J=5.5Hz), 7.03 (d, 2H, Ar-$\underline{H}$, $\underline{o}$ to NHAc, J=9Hz), 7.40 (d, 2H, Ar-$\underline{H}$, $\underline{m}$ to NHAc, J=9Hz), 9.25 (s, 2H, 2x$N\underline{H}$)

Analysis for : $C_{14}H_{20}N_4OS$ (292)

Calcd. : C, 54.10; H, 6.81; N, 15.41

Found : C, 53.68; H, 6.42; N, 15.82%.

Compounds 237 and 238 were prepared similarly from 222 and the corresponding piperazines.

N-(4-Amino-2-chlorophenyl)-1-methyl-4-piperazinylthiocarboxamide (239)

A hot solution of $FeSO_4$ (28 g) in ammonia (100 ml, d=0.88) and water (100 ml) was added to a hot solution of 230 (4.0 g, 0.0127 mol) in aqueous ammonia (250 ml, d=0.88). The reaction mixture was heated on water bath for 30 minutes and worked-up in usual manner. The resulting solid was recrystallized from ethyl acetate, yield 2.45 g (73%), m.p.180-5°.

IR(KBr) cm^{-1} : 2780, 2900 (C-H), 3150, 3250 (NH_2).

NMR($CDCl_3$ + DMSO-d_6) δ : 2.27 (s, 3H, N-CH_3), 2.42 (t, 4H, CH_3-N(CH_2)$_2$, J=5.5Hz), 3.94 (t, 4H, CSN(CH_2)$_2$, J=5.5Hz), 6.52 (dd, 1H, Ar-H, p to chloro, J=2.5 & 8Hz), 6.7 (d, 1H, Ar-H, o to chloro, J=2.5Hz), 7.0 (d, 1H, Ar-H, m to chloro, J=8Hz)

Analysis for : $C_{12}H_{17}ClN_4S$ (284.5)

Calcd. : C, 50.61; H, 5.97; N, 19.68

Found : C, 50.25; H, 6.35; N, 20.10%.

Similarly compounds 240-244 were prepared by reduction of the corresponding nitro compounds.

N-(4-Isothiocyanatophenyl)-1-phenyl-4-piperazinyl carboxamide (250)

A solution of thiophosgene (0.50 ml, 0.0064 mol) in acetone (50 ml) was added dropwise to a stirred solution of 244 (1.0 g, 0.0032 mol) in acetone (100 ml) during 30 minutes and the reaction mixture stirred at room temperature for 3 hr. Solvent was removed *in vacuo* and the residual solid was crystallized from chloroform-pet. ether, yield 0.71 g (65%), m.p.182-4°.

IR(KBr) cm^{-1} : 1635 (CO), 2050 (NCS), 2700, 2800 (C-H), 3250 (NH).

NMR($CDCl_3$ + DMSO-d_6) δ : 3.2 (t, 4H, $ArN(CH_2)_2$, J=5Hz), 3.74 (t, 4H, $CON(CH_2)_2$, J=5Hz), 6.8-7.6 (m, 9H, Ar-H), 8.55 (s, 1H, NH)

Analysis for : $C_{18}H_{18}N_4OS$ (338)

Calcd. : C, 63.90; H, 5.32

Found : C, 64.25; H, 5.76%.

Compounds 245-249 were prepared similarly from their respective amines 239-243 and thiophosgene.

N-(2-Benzimidazolyl)-N'-(4-nitrophenyl)thiourea (252)

A mixture of 2-aminobenzimidazole (251, 1.0 g, 0.0075 mol) and 219 (1.35 g, 0.0075 mol) in ethyl-acetate

(30 ml) was refluxed for 4 hr on a water bath. The reaction mixture was left overnight at room temperature and the crystallized yellow needles were filtered, washed with cold ethyl acetate (2x10 ml) and dried, yield 1.78 g (76%), m.p.243-4°.

IR(KBr) cm^{-1} : 1315, 1540 (NO_2), 3250 (NH).

Analysis for : $C_{14}H_{11}N_5O_2S$ (313)

Calcd. : C, 53.60; H, 3.51

Found : C, 53.26; H, 3.91%.

Similarly compound 253 was prepared by reaction of 2-aminobenzimidazole (251) and 220, yield 75.5%, m.p.218°.

IR(KBr) cm^{-1} : 1305, 1560 (NO_2), 3250 (NH).

Analysis for : $C_{14}H_{10}ClN_5O_2S$ (347.5)

Calcd. : C, 48.34; H, 2.88

Found : C, 48.72; H, 3.20%.

N-(2-Benzimidazolyl)-N'-(4-aminophenyl)thiourea (254)

A hot solution of $FeSO_4$ (7.0 g) in aqueous ammonia (50 ml, d=0.88) and water (50 ml) was added to a hot solution of 252 (1.0 g, 0.0032 mol) in ammonia (100 ml, d=0.88). The reaction mixture was heated on water bath for 30 minutes and worked-up as usual, yield 0.55 g (62%), m.p.86°.

IR(KBr) cm^{-1} : 3200, 3350 (NH_2).

Analysis for : $C_{14}H_{13}N_5S$ (283)

Calcd. : C, 59.36; H, 4.59

Found : C, 59.62; H, 4.81%.

N-(2-Benzimidazolyl)-N'-(4-isothiocyanatophenyl)urea.HCl(255)

A solution of thiophosgene (0.27 ml, 0.0035 mol) in acetone (20 ml) was added dropwise to a stirred solution of 254 (0.5 g, 0.0017 mol) in acetone (50 ml) at room temperature and the product isolated as usual as its hydrochloride, yield 0.4 g (65%), m.p.256-59°.

IR(KBr) cm^{-1} : 1625 (CO), 2040 (NCS), 3350 (NH).

Analysis for : $C_{15}H_{12}ClN_5OS$ (345.5)

Calcd. : C, 52.09; H, 3.47

Found : C, 51.75; H, 3.22%.

N-(2-Chloro-4-nitrophenyl)-N'-(4-acetylaminophenyl) thiourea (257)

A solution of 4-aminoacetanilide (0.7 g, 0.0046 mol) in acetone (20 ml) was added dropwise to a refluxing solution of 220 (1.0 g, 0.0046 mol) in acetone (30 ml). Refluxing was continued for 4 hr on a water bath. The solvent was removed in vacuo and the residual solid crystallized from acetone, yield 1.1 g (65%), m.p.218°.

IR(KBr) cm^{-1} : 1330, 1500 (NO_2), 1655 (CO), 3220 (NH).

NMR($CDCl_3$ + DMSO-d_6) δ : 2.05 (s, 3H, $COCH_3$), 7.42 (d, 2H, Ar-H, m to NHAc, J=9Hz), 7.62 (d, 2H, Ar-H,

o to NHAc, J=9Hz), 8.05-8.35 (m, 4H, Ar-H o and m to chloro), 8.7 (dd, 1H, Ar-H, p to chloro, J=3 & 9Hz)

Analysis for : $C_{15}H_{13}ClN_4O_3S$ (364.5)

Calcd. : C, 49.30; H, 3.59

Found : C, 48.92; H, 3.92%.

Similarly 256 was prepared from 219 and 4-aminoacetanilide in 78% yield, m.p.105°.

IR(KBr) cm^{-1} : 1300, 1500 (NO_2), 1655 (CO), 3200 (NH).

NMR($CDCl_3$ + $DMSO-d_6$) δ : 2.1 (s, 3H, $COCH_3$), 7.35 (d, 2H, Ar-H, o to NHAc, J=9Hz), 7.58 (d, 2H, Ar-H, m to NHAc, J=9Hz), 7.86 (d, 2H, Ar-H, m to NO_2, J=9Hz), 8.12 (d, 2H, Ar-H, o to NO_2, J=9Hz)

Analysis for : $C_{15}H_{14}N_4O_3S$ (330)

Calcd. : C, 54.54; H, 4.24

Found : C, 54.25; H, 4.58%.

The thioureas (258-260)[50-52], thiocarboxamide (264)[53] and thioamide (265)[54] were prepared by literature methods in good yields.

N-Phenyldiethylamino thiocarboxamide (261)

To a stirred solution of phenyl isothiocyanate (1.35 g, 0.01 mol) in benzene (20 ml) was added dropwise a solution of diethylamine (0.73 g, 0.01 mol) at room

temperature. Stirring was continued for 3 hr at same temperature and then heated on water bath for 10 minutes. The solvent was removed *in vacuo* to get viscous oil, yield 1.8 g (89%).

IR(neat) cm^{-1} : 1340, 1530 (NO_2).

NMR($CDCl_3$) δ : 1.08 (t, 3H, $CH_2\underline{CH}_3$, J=8Hz), 3.52 (q, 2H, $\underline{CH}_2CH_3$, J=8Hz), 7.1 (s, 5H, Ar-H)

Analysis for : $C_{11}H_{16}N_2S$ (208)

Calcd. : C, 65.00; H, 7.69

Found : C, 64.68; H, 7.28%.

Similarly 262 and 263 were prepared by action of piperidine and N-methylpiperazine on phenyl isothiocyanate in benzene.

The General method of desulphurization is illustrated by preparation of 267 from 258 and thiophosgene

A solution of 258 (1.21 g, 0.005 mol) in acetone (40 ml) was added dropwise during 30 minutes to a stirred solution of thiophosgene (0.44 ml, 0.005 mol) in acetone (15 ml) at room temperature. The reaction mixture was stirred for 2 hr and solvent removed. The residue crystallized from benzene, yield 0.85 g (75%), m.p.166-67° (lit.[55] m.p.167-8°).

Similarly other ureas and carboxamides (259-264) and amide 265 were prepared from their respective thio analogs (m.p., yield given).

268 (185°, lit.[56] m.p.184°, 75%), 269 (190°, lit.[57] m.p. 192°, 80%), 270 (85°, 76%), 271 (132°, 75%), 272 (167-69°, 85%), 273 (116°, lit.[58] m.p.118-19°, 80%) and amide 274 (60°, lit.[59] m.p.61°, 75%).

All the ureas and carboxamides (267-273) were prepared by reaction of the corresponding isocyanates and amines. The amide 274 was obtained by action of acetic anhydride on benzylamine.

1-Methyl-4-[(N-phenyl-N'-cyclohexyl) amidino]piperazine (275)

To a stirred solution of 271 (1.0 g, 0.0042 mol) and triethylamine (0.86 g, 0.0084 mol) in dry acetone (25 ml) was added dropwise a solution of thiophosgene (0.36 ml, 0.0042 mol) when addition was complete, N-methyl-piperazine (0.42 g, 0.0042 mol) in dry acetone (10 ml) was added dropwise with constant stirring. Stirring was continued for 2 hr at room temperature and solvent removed *in vacuo*. The product was chromatographed over silica gel column using benzene as eluant, yield 0.26 g (20.3%), m.p.240°.

IR(KBr) cm^{-1} : 1630 (C=N), 2680, 2740, 2950 (C-H), 3320 (NH).

Analysis for : $C_{18}H_{28}N_4$ (300)

Calcd. : C, 72.00; H, 9.30

Found : C, 72.40; H, 8.95%.

N-(4-Nitrophenyl)piperazine (276)

A mixture of anhydrous piperazine (5.0 g, 0.058 mol), 4-chloronitrobenzene (18.3 g, 0.116 mol) and potassium carbonate (8.1 g, 0.058 mol) in dry acetone (100 ml) was heated in steel bomb for 15 hr at 120-30°. The reaction mixture was cooled, potassium carbonate filtered out and solvent was removed *in vacuo*. The crude product was chromatographed over silica gel column using ethyl acetate and 10% methanol in ethyl acetate as eluant. The unreacted 4-chloro nitrobenzene (5 g) was recovered, yield 6.5 g (54.1%), m.p.125°.

IR(KBr) cm^{-1} : 1300, 1580 (NO_2), 2800, 2900 (C-H), 3300 (NH).

Mass at m/z : 207 (M^+)

NMR($CDCl_3$ + DMSO-d_6) δ : 1.7 (bs, 1H, NH), 2.9 (t, 4H, $HN(CH_2)_2$, J=6Hz), 3.27 (t, 4H, Ar-$N(CH_2)_2$, J=6Hz), 6.64 (d, 2H, Ar-H, m to NO_2, J=9Hz), 7.93 (d, 2H, Ar-H, o to NO_2, J=9Hz)

Analysis for : $C_{10}H_{13}N_3O_2$ (207)

Calcd. : C, 57.97; H, 6.28

Found : C, 58.42; H, 6.68%.

1-(4-Nitrobenzoyl)-4-(4-nitrophenyl)piperazine (278)

To a solution of 276 (0.5 g, 0.0024 mol) in dry

benzene (30 ml) was added dropwise at room temperature a solution of 4-nitrobenzoylchloride (0.5 g, 0.0026 mol) in dry benzene (20 ml) with constant stirring. Stirring was continued for 2 hr at room temperature and then reaction mixture was refluxed for 3 hr. It was then cooled and washed successively with 5% $NaHCO_3$ solution (3x20 ml), water (3x20 ml) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue crystallized from ethanol, yield 0.6 g, (70%), m.p.174-5°.

IR(KBr) cm^{-1} : 1320, 1520 (NO_2), 1600 (Arom), 1635 (CO).

NMR($CDCl_3$ + DMSO-d_6) δ : 3.5 (bs, 4H, ArN(CH_2)$_2$), 3.65 (bs, 4H, ArCON(CH_2)$_2$), 6.82 (d, 2H, Ar-H, o to N(CH_2)$_2$, J=9Hz), 7.6 (d, 2H, Ar-H, o to NCO, J=9Hz), 8.0 (d, 2H, Ar-H, o to NO_2, J=8.5Hz), 8.2 (d, 2H, Ar-H, m to NCO, J=9Hz)

Analysis for : $C_{17}H_{16}N_4O_5$ (356)

Calcd. : C, 57.30; H, 4.38

Found : C, 57.75; H, 4.66%.

1-(4-Aminobenzoyl)-4-(4-aminophenyl)piperazine (279)

To a hot solution of 278 (0.5 g, 0.0014 mol) in acetone (30 ml) and aqueous ammonia solution (30 ml) was added a hot solution of ferrous sulfate (4 g) in water

(20 ml) and aqueous ammonia solution (30 ml, d=0.88). The reaction mixture was heated at water bath for 30 minutes and reaction worked-up as usual. The product was recrystallized from benzene, yield 0.2 g (50%), m.p.126-7°.

IR(KBr) cm^{-1} : 1585 (Arom), 1620 (NCO), 3300, 3400 (NH_2).

Mass at m/z : 296 (M^+)

NMR($CDCl_3$ + DMSO-d_6) δ : 2.92 (t, 4H, ArN($C\underline{H}_2$)$_2$, J=6Hz), 3.65 (t, 4H, ArCON($C\underline{H}_2$)$_2$, J=6Hz), 6.4-6.72 (m, 6H, Ar-$\underline{H}$), 7.14 (d, 2H, Ar-$\underline{H}$, $\underline{o}$ to NCO, J=9Hz)

Analysis for : $C_{17}H_{20}N_4O$ (296)

Calcd. : C, 68.91; H, 6.75

Found : C, 69.38; H, 6.45%.

1-(4-Isothiocyanatobenzoyl)-4-(4-isothiocyanatophenyl) piperazine (280)

Thiophosgene (0.25 ml, 0.0032 mol) in acetone (20 ml) was added dropwise to a stirred solution of 279 (0.5 g, 0.0016 mol) in acetone (20 ml) at room temperature. The stirring was continued for 4 hr. The separated hydrochloride was filtered, washed with acetone (3x10 ml) and dried. Free base was obtained by treatment with triethylamine, yield 0.42 g (65.6%), m.p.125°.

IR(KBr) cm^{-1} : 1635 (CO), 2100 (NCS).

NMR(DMSO-d_6) δ : 3.15-3.30 (m, 4H, $N(C\underline{H}_2)_2$), 3.45-3.62 (m, 4H, $CON(C\underline{H}_2)_2$), 6.86-7.8 (m, 8H, Ar-H).

Analysis for : $C_{19}H_{16}N_4OS_2$ (380)

Calcd. : C, 60.00; H, 4.21

Found : C, 60.32; H, 4.10%.

1,4-Di-(4-nitrobenzoyl)piperazine (281)

To a stirred solution of 4-nitrobenzoyl chloride (4.5 g, 0.0242 mol) and triethylamine (2.35 g, 0.0232 mol) in dry benzene (50 ml), was added dropwise a solution of anhydrous piperazine (1.0 g, 0.012 mol) in dry benzene at room temperature during 30 minutes. Stirring was continued for 5 hr at room temperature and the solid separated was filtered, washed with 5% $NaHCO_3$ solution (5x20 ml) and water (3x20 ml) and dried, yield 4.0 g (89.4%), m.p. $>300^{\circ}$.

IR(KBr) cm^{-1} : 1350, 1510 (NO_2), 1630 (CO), 2650, 2720, 2900 (C-H).

Mass at m/z : 384 (M^+)

Analysis for : $C_{18}H_{16}N_4O_6$ (384)

Calcd. : C, 56.25; H, 4.16

Found : C, 56.62; H, 3.84%.

1,4-Di-(4-aminobenzoyl)piperazine (282)

A suspension of 281 (1.0 g, 0.0026 mol) and Raney-nickel (~ 0.2 g) in ethanol-THF mixture (1:1, 100 ml) was hydrogenated in a Paar hydrogenator at 3.5 kg/cm^2 of hydrogen for 6 hr and the product worked-up as usual which was recrystallised from ethanol, yield 0.58 g (69%), m.p.250°.

IR(KBr) cm^{-1} : 1590 (Arom), 1620 (CO), 3300, 3420 (NH_2).

Mass at m/z : 324 (M^+)

NMR(DMSO-d_6) δ : 3.52 [s, 8H, $N(C\underline{H}_2)_4$], 5.5 (s, 4H, 2x$N\underline{H}_2$), 6.52 (d, 4H, Ar-$\underline{H}$, $\underline{o}$ to NH_2, J=9Hz), 7.2 (d, 4H, Ar-$\underline{H}$, $\underline{m}$ to NH_2, J=9Hz)

Analysis for : $C_{16}H_{20}N_4O_2$ (324)

Calcd. : C, 66.66; H, 6.17

Found : C, 67.12; H, 5.92%.

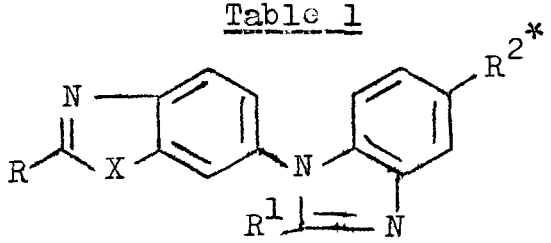
1,4-Di-(4-Isothiocyanatobenzoyl)piperazine (283)

A solution of thiophosgene (0.24 ml, 0.0031 mol) in chloroform (30 ml) was added dropwise to a stirred solution of 282 (0.5 g, 0.0015 mol) in 10% aqueous hydrochloric acid (30 ml) at room temperature during 30 minutes. Stirring was continued for 4 hr at room temperature and the chloroform layer was separated from aqueous layer. It was washed with water (3x10 ml), dried

(Na_2SO_4) and the solvent removed *in vacuo*. The residual solid was triturated with hexane to get a pure product, yield 0.36 g (57.1%), m.p.220°.

IR(KBr) cm^{-1}	: 1625 (CO), 2100 (NCS)
Mass at m/z	: 408 (M^+)
NMR($CDCl_3$ + DMSO-d_6) δ	: 3.55 [s, 8H, $N(C\underline{H}_2)_4$], 7.22-7.7 (m, 8H, Ar-$\underline{H}$).
Analysis for	: $C_{20}H_{16}N_4O_2S_2$ (408)
Calcd.	: C, 58.82; H, 3.92
Found	: C, 58.46; H, 4.26%.

Table 1

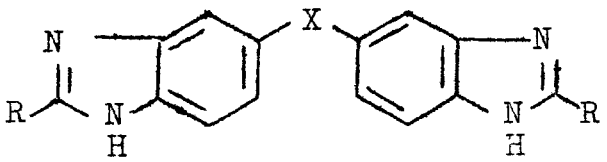


Compd. No.	R	X	R^1	Molecular formula (Mol.Wt.)	m.p. °C	Yield %	Analysis(%) Calcd.	Analysis(%) Found	Spectral data
1	2	3	4	5	6	7	8	9	10
34	CH_3	NH	H	$C_{16}H_{13}N_5O$ (291)	>300	65	C: 65.97 H: 4.46 N: 24.05	66.32 4.15 23.82	IR(KBr) cm^{-1}: 1665 (CO). NMR(TFA)δ: 2.65 (s, 3H, C-C<u>H</u>$_3$), 7.2-8.70 (m, 7H, Ar-<u>H</u> & N=C<u>H</u>-N).
35	CH_3	NH	CH_3	$C_{18}H_{17}N_5O$ (319)	88-90	60	C: 67.71 H: 5.32 N: 21.94	67.34 5.68 22.38	IR(KBr) cm^{-1}: 1665 (CO). NMR(TFA)δ: 2.08 (s, 3H, COC<u>H</u>$_3$), 2.48 (s, 3H, N=C(N-)-C<u>H</u>$_3$), 2.7 (s, 3H, N=C(NH)-C<u>H</u>$_3$), 6.95-7.95 (m, 6H, Ar-<u>H</u>).
45	CH_3	S	SH	$C_{16}H_{10}N_4S_3$ (354)	>300	60	C: 54.23 H: 2.89	53.86 3.22	IR(KBr) cm^{-1}: 2100 (NCS).

1	2	3	4	5	6	7	8	9	10
49	CH_3	S	H	$C_{16}H_{12}N_4OS$ (308)	108-9	65	C: 62.33 H: 3.89	62.68 3.56	IR(KBr) cm^{-1}: 1655 (CO), 3250 (NH). NMR(DMSO-d_6)δ: 2.78 (s, 3H, C-CH_3), 7.44-8.44 (m, 8H, Ar-H and HCO).
50	CH_3	S	CH_3	$C_{18}H_{16}N_4OS$ (336)	218-20	62	C: 64.28 H: 4.78	63.81 4.38	IR(KBr) cm^{-1}: 1675 (CO), 3250 (NH). NMR(DMSO-d_6)δ: 2.05 (s, 3H, $COCH_3$), 2.42 (s, 3H, N=C(N-)CH_3), 2.82 (s, 3H, N=C(S)-CH_3), 7.05-8.25 (m, 7H, Ar-H and NH).

*R^2 = $NHCOR^1$ in all compounds except 45 where R^2 = NCS

Table 2



Compd. No.	R	X	Molecular formula (Mol.Wt.)	m.p. °C	Yield %	Analysis(%)	Calcd.	Found	Spectral data
1	2	3	4	5	6	7	8		9
61	CH_3	S	$C_{16}H_{14}N_4S$ (294)	155	67	C:	65.30	65.74	IR(KBr) cm^{-1}: 1600 (Arom), 2800-2900 (C-H), 3400(NH). NMR(DMSO-d_6)δ: 2.47 (s, 6H, 2xC-C<u>H</u>$_3$), 6.8-7.4 (m, 6H, Ar-<u>H</u>).
						H:	4.76	5.20	
						N:	19.05	19.45	
63	$NHCOOC_2H_5$	S	$C_{20}H_{20}N_6O_4S$ (440)	280	62	C:	54.54	54.88	IR(KBr) cm^{-1}: 1600 (Arom), 1705 (CO), 2700-2800 (C-H), 3340 (NH). NMR(DMSO-d_6)δ: 1.3 (t, 3H, $CH_2C\underline{H}_3$, J=6Hz), 4.22 (q,
						H:	4.54	4.08	
						N:	19.09	18.72	

1	2	3	4	5	6	7	8	9
								2H, $C\underline{H}_2CH_3$, J=6Hz), 6.9-7.5 (m, 6H, Ar-$\underline{H}$).
70	CH_3	SO_2	$C_{16}H_{14}N_4O_2S$ (326)	195-7	64	C: 58.89 59.27 H: 4.29 4.62 N: 17.18 16.72		IR(KBr) cm^{-1}: 1160 (SO_2), 1610 (Arom), 3200-3300 (NH). NMR(DMSO-d_6)δ: 2.42 (s, 6H, 2xC-$C\underline{H}_3$), 7.5 (s, 4H, Ar-$\underline{H}$), 7.92 (d, 2H, Ar-$\underline{H}$, J=2Hz).
72	$NHCOOC_2H_5$	SO_2	$C_{20}H_{20}N_6O_6S$ (472)	280	58	C: 50.85 51.32 H: 4.24 4.70 N: 17.80 18.15		IR(KBr)cm^{-1}: 1140 (SO_2), 1600 (Arom), 1730 (CO), 2780-2850 (C-H), 3380 (NH). NMR(DMSO-d_6)δ: 1.2 (t,6H, 2x$CH_2C\underline{H}_3$,J=6Hz), 4.25 (q, 4H, 2x$C\underline{H}_2CH_3$,J=6Hz), 7.6 (s, 4H, Ar-$\underline{H}$), 7.95 (d, 2H, Ar-$\underline{H}$, J=2Hz).

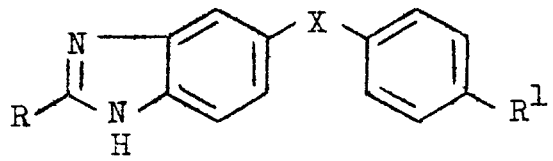
1	2	3	4	5	6	7	8	9
82	$NHCOOC_2H_5$	CO	$C_{21}H_{20}N_6O_5$ (436)	>280	64	C: 57.80 H: 4.59 N: 19.27	58.18 4.76 19.55	IR(KBr)cm^{-1}: 1600 (Arom), 1640, 1720 (CO), 2700-3000 (C-H), 3350 (NH). NMR(TFA)δ: 0.8-1.2 (m, 6H, 2x$CH_2\underline{CH_3}$), 3.9-4.3 (m, 4H, 2x$\underline{CH_2}CH_3$), 7.2-8.0 (m, 6H, Ar-H).
89	CH_3	CO	$C_{17}H_{14}N_4O$ (290)	108-10	52	C: 70.34 H: 4.83 N: 19.31	70.72 5.25 19.48	IR(KBr)cm^{-1}: 1600 (Arom), 1640 (CO), 3100-3200 (NH). NMR(TFA)δ: 2.62 (s, 6H, 2xC-$C\underline{H_3}$), 7.56-8.0 (m, 6H, Ar-H).
91	$NHCOOC_2H_5$	CH_2	$C_{21}H_{22}N_6O_4$ (422)	>280	60	C: 59.71 H: 5.21	59.48 5.68	IR(KBr)cm^{-1}: 1590 (Arom), 1710 (CO), 2650-2900 (C-H), 3300 (NH). NMR(TFA)δ: 1.0 (t, 6H, 2x$CH_2\underline{CH_3}$, J=8Hz), 3.82 (s,

1	2	3	4	5	6	7	8	9
								2H, $ArC\underline{H}_2$-Ar), 4.04 (q, 4H, $2xC\underline{H}_2CH_3$, J=8Hz), 6.9-7.3 (m, 6H, Ar-$\underline{H}$).
93	CH_3	CH_2	$C_{17}H_{16}N_4$ (276)	165-6	55.5	C: 73.91 H: 5.80	74.34 6.22	IR(KBr)cm^{-1}: 1620 (Arom), 3400-3000 (NH) Mass: at m/z 276 (M^+) NMR(TFA)δ: 2.5 (s, 6H, 2x C-$C\underline{H}_3$), 3.92 (s, 2H, $ArC\underline{H}_2$ Ar), 7.0-7.5 (m, 6H, Ar-$\underline{H}$).
108	H	O	$C_{14}H_{10}N_4O$ (250)	135-6	68	C: 67.20 H: 4.00 N: 22.40	67.45 4.24 22.75	IR(KBr)cm^{-1}: 1600, (Arom), 3100 (NH). Mass at m/z 250 (M^+) NMR(DMSO-d_6)δ: 6.8-7.8 (m, 6H, Ar-$\underline{H}$), 8.3 (s, 2H, 2x N=C$\underline{H}$-NH).
109	CH_3	O	$C_{16}H_{14}N_4O$ (278)	115-7	54	C: 69.06 H: 5.04 N: 20.14	68.68 5.42 20.28	IR(KBr) cm^{-1}: 1600 (Arom), 3100 (NH). Mass at m/z 278 (M^+)

1	2	3	4	5	6	7	8	9
111	$NHCOOC_2H_5$	O	$C_{20}H_{20}N_6O_5$ (424)	>280	60	C: 56.60 H: 4.72 N: 19.81	56.80 4.40 20.25	IR(KBr)cm^{-1}: 1600 (Arom), 1700 (CO), 2700-2950 (C-H), 3320 (NH). NMR(TFA)δ: 0.98 (t, 6H, $2xCH_2\underline{CH}_3$, J=7Hz), 4.0 (q, 4H, $2xC\underline{H}_2CH_3$, J=7Hz), 6.75-8.25 (m, 6H, Ar-H)
116	$NHCOOC_2H_5$	SCH_2CH_2S	$C_{22}H_{24}N_6O_4S_2$ (500)	>280	58	C: 52.80 H: 4.80 N: 16.80	53.16 4.42 17.05	IR(KBr)cm^{-1}: 1600(Arom), 1705 (CO), 2700-3000 (C-H), 3360 (NH). NMR(TFA)δ: 0.98 (t, 6H, $2xCH_2\underline{CH}_3$, J=7Hz), 2.72 (s, 2H, $S(C\underline{H}_2)_2S$), 4.02 (q, 4H, $2xC\underline{H}_2CH_3$, J=7Hz), 7.0-7.2 (m, 6H, Ar-H).

1	2	3	4	5	6	7	8	9
124	$NHCOOC_2H_5$		$C_{26}H_{28}N_8O_6$ (548)	>280	45	C: 53.93 H: 5.11 N: 20.44	54.16 5.18 20.16	IR(KBr)cm^{-1}: 1600 (Arom), 1720 (CO), 2750-2950 (C-H), 3380 (NH). NMR(TFA)δ: 1.02 (t, 6H, 2x$CH_2\underline{CH}_3$, J=7Hz), 3.4-3.6 (m, 8H, 4x$NC\underline{H}_2$), 4.0 (q, 4H, 2x$C\underline{H}_2CH_3$, J=7Hz), 6.9-7.6 (m, 6H, Ar-H).

Table 3



Compd. No.	R	R^1	X	Molecular formula (Mol.Wt.)	m.p. °C	Yield %	Analysis(%) Calcd.	Analysis(%) Found	Spectral data IR:KBr in cm^{-1};NMR ppm (δ)
1	2	3	4	5	6	7	8	9	10
150	$NHCOOCH_3$	NHAc	S	$C_{17}H_{16}N_4O_3S$ (370)	280	68.5	C: 57.30 H: 4.77 N: 15.73	57.65 5.15 15.28	IR: 1660, 1710 (CO), 3300-3400 (NH). NMR(TFA): 2.02 (s, 3H, $COCH_3$), 3.56 (s, 3H, OCH_3), 6.85-7.2 (m, 7H, Ar-H)
152	H	NHAc	S	$C_{15}H_{13}N_3OS$ (283)	160	72.5	C: 63.60 H: 4.59 N: 14.87	63.32 4.88 15.30	IR: 1660 (CO), 3100-3250 (NH). NMR(DMSO-d_6): 2.02 (s, 3H, $COCH_3$), 7.0-7.55 (m, 7H, Ar-H), 8.06 (s, 1H, N=CH-N).

1	2	3	4	5	6	7	8	9	10
154	$NHCOOCH_3$	NH_2	S	$C_{15}H_{14}N_4O_2S$ (314)	220-22	80	C: 57.34 H: 4.45 N: 17.85	57.68 4.22 17.52	IR: 1700 (CO), 3400 (NH,NH_2) NMR(TFA) 3.55 (s, 3H, OCH_3), 6.9-7.3 (m, 7H, Ar-H).
155	$NHCOOC_2H_5$	NH_2	S	$C_{16}H_{16}N_4O_2S$ (328)	246	79.5	C: 58.53 H: 4.87 N: 17.07	58.21 5.21 16.64	IR: 1700 (CO), 3100, 3350 (NH,NH_2) NMR(TFA) 1.0 (t, 3H, CH_2CH_3, J=7Hz), 4.02 (q, 2H, CH_2CH_3, J=7Hz), 6.8-7.25 (m,7H,Ar-H).
156	H	NH_2	S	$C_{13}H_{11}N_3S$ (241)	135	64	C: 64.73 H: 4.56 N: 17.42	64.38 4.82 17.66	IR: 3300 (NH_2). NMR(DMSO-d_6) 5.3 (hump, 2H, NH_2), 6.55 (d, 2H, Ar-H; o to NH_2, J=7Hz), 6.9-7.5 (m, 6H, Ar-H & NH), 8.1 (s, 1H, N=CH-N).
157	CH_3	NH_2	S	$C_{14}H_{13}N_3S$ (255)	80	66.6	C: 65.88 H: 5.09 N: 16.47	66.26 5.50 16.22	IR: 3000-3400 (NH,NH_2). NMR(TFA) 2.5 (s, 3H, C-CH_3), 6.95 (s, 4H, Ar-H), 7.16-7.4 (m, 3H, Ar-H).

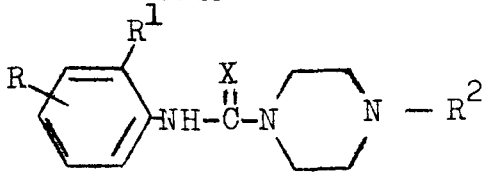
1	2	3	4	5	6	7	8	9	10
165	NH_2	NH_2	SO_2	$C_{13}H_{12}N_4SO_2$ (298)	250	85.3	C: 52.35 H: 4.03 N: 18.80	52.68 4.26 19.16	IR: 1140 (SO_2), 1660 (C=N), 3100-3400 (NH,NH_2). Mass at m/z 288 (M^+)
166	H	NH_2	SO_2	$C_{13}H_{11}N_3O_2S$ (273)	274	71	C: 57.14 H: 4.03 N: 15.38	57.47 4.45 15.76	IR: 1150 (SO_2), 3300-3500 (NH,NH_2). NMR(DMSO-d_6) 6.02 (s, 2H, $N\underline{H}_2$), 6.6 (d, 2H, Ar-$\underline{H}$, o to NH_2, J=8Hz), 7.48-8.4 (m, 6H, Ar-$\underline{H}$ & N=C$\underline{H}$-N).
168	$NHCOOCH_3$	NCS	S	$C_{16}H_{12}N_4O_2S_2$ (356)	230-32	72	C: 53.93 H: 3.37 N: 15.53	54.38 3.65 15.78	IR: 1705 (CO), 2100 (NCS), 3400 (NH). NMR(TFA) 3.75 (s, 3H, $OC\underline{H}_3$), 7.0-7.65 (m, 7H, Ar-$\underline{H}$).
169	$NHCOOC_2H_5$	NCS	S	$C_{17}H_{14}N_4O_2S_2$ (370)	222	74	C: 55.13 H: 3.78 N: 15.13	55.28 4.12 14.82	IR: 1700 (CO), 2100 (NCS), 3350 (NH). NMR(TFA) 1.26 (s, 3H, $CH_2C\underline{H}_3$, J=7Hz), 4.2 (q, 2H, $C\underline{H}_2CH_3$, J=7Hz), 6.95-7.55(m, 7H, Ar-$\underline{H}$).

1	2	3	4	5	6	7	8	9	10
170	H	NCS	S	$C_{14}H_9N_3S_2$ (283)	190-91	62	C: 59.36 H: 3.18 N: 14.84	59.25 3.62 15.18	IR: 2080 (NCS), 3050-3100(NH)
171	CH_3	NCS	S	$C_{15}H_{11}N_3S_2$ (297)	196-8	64.4	C: 60.40 H: 3.70 N: 14.14	60.52 3.82 14.40	IR: 2100 (NCS), 3400 (NH). NMR(TFA) 2.5 (s, 3H, C-CH_3), 6.5-7.5 (m, 7H, Ar-H).
172	$NHCOOCH_3$	NCS	SO_2	$C_{16}H_{12}N_4O_4S_2$ (388)	>280	65.3	C: 49.48 H: 3.09	49.28 3.44	IR: 1140 (SO_2), 1720 (CO), 2030 (NCS), 3360 (NH) NMR(TFA) 3.58 (s, 3H, OCH_3), 6.85-7.9 (m, 7H, Ar-H).
173	$NHCOOC_2H_5$	NCS	SO_2	$C_{17}H_{14}N_4O_4S_2$ (402)	>280	68	C: 50.75 H: 3.48	50.62 3.65	IR: 1150 (SO_2), 1720 (CO), 2080 (NCS), 3400 (NH). NMR(TFA) 1.0 (t, 3H, CH_2CH_3, J=6Hz), 4.02 (q, 2H, CH_2CH_3, J=6Hz), 6.9-7.9(m, 7H, Ar-H).
174	H	NCS	SO_2	$C_{14}H_9N_3O_2S_2$ (315)	148-9	62.5	C: 53.33 H: 2.86	53.14 3.08	IR: 1160 (SO_2), 2080 (NCS).
179	$NHCOOC_2H_5$	NHAc	O	$C_{18}H_{18}N_4O_4$ (354)	>280	78	C: 61.02 H: 5.08 N: 15.82	60.56 4.72 15.48	IR:1650,1700(CO),3330(NH). NMR(TFA) 1.0 (t, 3H, CH_2CH_3, J=7Hz), 2.08 (s, 3H, $COCH_3$),

1	2	3	4	5	6	7	8	9	10
									4.03 (q, 2H, $C\underline{H}_2CH_3$, J=7Hz), 6.5-7.25 (m, 7H, Ar-$\underline{H}$).
181	$NHCOOC_2H_5$	NH_2	0	$C_{16}H_{16}N_4O_3$ (312)	>280	76	C: 61.54 H: 5.13 N: 17.95	61.32 5.62 17.85	IR: 1710 (CO), 3460 (NH). NMR(TFA) 1.0 (t, 3H, $CH_2C\underline{H}_3$, J=8Hz), 4.04 (q, 2H, $C\underline{H}_2CH_3$, J=8Hz), 6.6-7.25 (m, 7H, Ar-$\underline{H}$).
183	CH_3	NHAc	0	$C_{16}H_{15}N_3O_2$ (281)	205-6	66.6	C: 68.33 H: 5.34 N: 14.95	68.62 5.48 15.36	IR: 1660 (CO), 3280 (NH). NMR(TFA) 2.1 (s, 3H, $COC\underline{H}_3$), 2.5 (s, 3H, C-$C\underline{H}_3$), 6.75-7.3 (m, 7H, Ar-$\underline{H}$).
185	CH_3	NH_2	0	$C_{14}H_{13}N_3O$ (239)	65-7	64.5	C: 70.29 H: 5.44 N: 17.57	70.12 5.34 17.38	IR: 3400 (NH_2). NMR(TFA) 2.5 (s, 3H, C-$C\underline{H}_3$), 6.7-7.35 (m, 7H, Ar-$\underline{H}$).
187	$NHCOOC_2H_5$	NCS	0	$C_{17}H_{14}N_4O_3S$ (354)	212	72.5	C: 57.63 H: 3.95 N: 15.82	57.96 3.62 15.74	IR: 1700 (CO), 2100 (NCS), 3350 (NH). NMR(TFA) 1.0(t, 3H, $CH_2C\underline{H}_3$, J=7Hz), 4.04 (q, 2H, $C\underline{H}_2CH_3$, J=7Hz), 6.5-7.3 (m, 7H, Ar-$\underline{H}$).

1	2	3	4	5	6	7	8	9	10
188	H	NCS	0	$C_{14}H_9N_3OS$ (267)	178-9	63.5	C: 62.90 H: 3.37 N: 15.73	63.16 3.72 15.88	IR: 2100 (NCS), 3400 (NH).
189	CH_3	NCS	0	$C_{15}H_{11}N_3OS$ (281)	215-6	58.0	C: 64.06 H: 3.91 N: 14.95	64.44 4.28 15.24	IR: 2080 (NCS), 3400 (NH). NMR(TFA) 2.5 (s, 3H, C-$\underline{CH}_3$), 6.5-7.3 (m, 7H, Ar-$\underline{H}$).

Table 4: Physical Data of Compounds



Compd. No.	R	R^1	R^2	X	Molecular formula (Mol.Wt.)	m.p. °C	Yield %	Analysis (%)	Calcd.	Found
1	2	3	4	5	6	7	8		9	10
225	4-NCS	H	CH_2Ph	S	$C_{19}H_{20}N_4S_2$ (368)	170-74	70.5	C:	61.96	62.35
								H:	5.43	5.08
								N:	15.22	15.46
226	4-NCS	H	$COOC_2H_5$	S	$C_{15}H_{18}N_4O_2S_2$ (350)	110-15	67.0	C:	51.43	51.65
								H:	5.14	5.46
								N:	16.00	16.32
228	4-NO_2	H	CH_2Ph	S	$C_{18}H_{20}N_4O_2S$ (356)	145	82.6	C:	60.67	60.82
								H:	5.62	5.46
								N:	15.73	15.52
229	4-NO_2	H	Ph	S	$C_{17}H_{18}N_4O_2S$ (342)	167-8	75.6	C:	59.65	59.52
								H:	5.26	5.64
								N:	16.37	16.24
230	4-NO_2	Cl	CH_3	S	$C_{12}H_{15}ClN_4O_2S$ (314.5)	126	77.0	C:	45.79	46.12
								H:	4.77	4.85
								N:	17.16	17.38
231	4-NO_2	Cl	CH_2Ph	S	$C_{18}H_{19}ClN_4O_2S$ (390.5)	136-8	77.1	C:	55.31	55.68
								H:	4.86	4.66
								N:	14.34	14.18

1	2	3	4	5	6	7	8		9	10
232	4-NO_2	Cl	Ph	S	$C_{17}H_{17}ClN_4O_2S$ (376.5)	172-4	73.1	C: H: N:	54.18 4.51 14.87	53.75 4.10 15.25
233	3-NO_2	H	CH_3	S	$C_{12}H_{16}N_4O_2S$ (280)	135	80.2	C: H: N:	51.43 5.71 20.00	51.08 5.26 20.38
234	3-NO_2	H	CH_2Ph	S	$C_{18}H_{20}N_4O_2S$ (356)	95	86	C: H: N:	60.67 5.62 15.73	60.42 5.85 15.78
235	3-NO_2	H	Ph	S	$C_{17}H_{18}N_4O_2S$ (342)	162-5	74.0	C: H: N:	59.65 5.26 16.37	59.46 5.52 16.48
237	4-NHAc	H	CH_2Ph	S	$C_{20}H_{24}N_4OS$ (368)	200-202	68	C: H: N:	65.22 6.52 15.22	65.48 6.76 15.30
238	4-NHAc	H	COOEt	S	$C_{16}H_{22}N_4O_3S$ (350)	156	70.5	C: H: N:	54.86 6.28 16.00	55.26 6.35 16.45
240	4-NH_2	Cl	CH_2Ph	S	$C_{18}H_{21}ClN_4S$ (360.5)	171-2	70.3	C: H: N:	59.92 5.82 15.53	60.25 5.62 15.28
241	4-NH_2	Cl	Ph	S	$C_{17}H_{19}ClN_4S$ (336.5)	240-42	66.6	C: H: N:	60.62 5.65 16.64	60.18 5.42 16.38

1	2	3	4	5	6	7	8		9	10
242	4-NH_2	H	CH_3	S	$C_{12}H_{18}N_4S$ (250)	100-103	75.0	C: H: N:	57.60 7.20 22.40	58.05 7.44 22.62
243	4-NH_2	H	CH_2Ph	S	$C_{18}H_{22}N_4S$ (326)	160	68.0	C: H: N:	66.26 6.75 17.18	66.45 7.10 17.28
244	4-NH_2	H	Ph	S	$C_{17}H_{20}N_4S$ (312)	240	55.0	C: H: N:	65.38 6.41 17.95	65.62 6.26 18.32
245	4-NCS	Cl	CH_3	O	$C_{13}H_{15}ClN_4OS.HCl$ (347)	212-4	71.0	C: H: N:	44.96 4.61 16.14	45.25 4.35 16.24
246	4-NCS	Cl	CH_2Ph	O	$C_{19}H_{19}ClN_4OS.HCl$ (423)	195-8	69.0	C: H: N:	53.90 4.73 13.24	54.32 4.65 13.46
247	4-NCS	Cl	Ph	O	$C_{18}H_{17}ClN_4OS$ (372.5)	190	64.2	C: H: N:	57.99 4.56 15.03	58.28 4.66 15.18
248	4-NCS	H	CH_3	O	$C_{13}H_{16}N_4OS.HCl$ (312.5)	217-8	67.3	C: H: N:	49.92 5.44 17.92	50.26 5.05 18.22
249	4-NCS	H	CH_2Ph	O	$C_{19}H_{20}N_4OS.HCl$ (388.5)	230-34	66.6	C: H: N:	58.69 5.40 14.41	59.12 5.80 14.65

Table 4 - Spectral Data

Compd. No.	IR:KBr in cm^{-1}, NMR ppm (δ)
1	2
225	IR: 2100 (NCS), 2800, 2900 (C-H), 3150-3400 (NH). NMR($CDCl_3$) 2.5 (t, 4H, $N(C\underline{H}_2)_2$, J=5Hz), 3.52 (s, 2H, $C\underline{H}_2C_6H_5$), 3.85 (t, 4H, $CSN(C\underline{H}_2)_2$, J=5Hz), 7.1-7.4 (m, 9H, Ar-$\underline{H}$).
226	IR: 1700 (CO), 2080 (NCS), 2850-2960 (C-H), 3150 (NH). NMR($CDCl_3$ + DMSO-d_6) 1.18 (t, 3H, $CH_2C\underline{H}_3$, J=7Hz), 3.44 (t, 4H, $CON(C\underline{H}_2)_2$, J=5Hz), 3.86 (t, 4H, $CSN(C\underline{H}_2)_2$, J=5Hz), 4.02 (q, 2H, $C\underline{H}_2CH_3$, J=7Hz), 7.0-7.3 (m, 4H, Ar-$\underline{H}$).
228	IR: 1340, 1540 (NO_2), 1600 (Arom), 2800, 2900 (C-H), 3300 (NH). NMR($CDCl_3$) 2.51 (t, 4H, $N(C\underline{H}_2)_2$, J=5.5Hz), 3.42 (s, 2H, $C\underline{H}_2C_6H_5$), 3.76 (t, 4H, $CSN(C\underline{H}_2)_2$, J=5.5Hz), 7.09 (d, 2H, Ar-$\underline{H}$, m to NO_2, J=9Hz), 7.16 (s, 5H, Ar-$\underline{H}$, $CH_2C_6\underline{H}_5$), 7.95 (d, 2H, Ar-$\underline{H}$, o to NO_2, J=9Hz).
229	IR: 1340, 1500 (NO_2), 1600 (Arom). NMR($CDCl_3$+DMSO-d_6) 3.18 (t, 4H, $N(C\underline{H}_2)_2$, J=5.5Hz), 3.98 (t, 4H, $CSN(C\underline{H}_2)_2$, J=5.5Hz), 7.15 (s, 5H, Ar-$\underline{H}$, N-$C_6\underline{H}_5$), 7.42 (d, 2H, Ar-$\underline{H}$, m to NO_2, J=9Hz), 7.95 (d, 2H, Ar-$\underline{H}$, o to NO_2, J=9Hz).

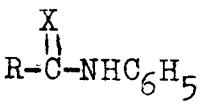
1	2
230	IR: 1300, 1510 (NO_2), 2800 (C-H), 3240 (NH). NMR($CDCl_3$) 2.34 (s, 3H, N-CH_3), 2.55 (t, 4H, N(CH_2)$_2$, J=5Hz), 3.98 (t, 4H, CSN(CH_2)$_2$, J=5Hz), 8.10-8.34 (m, 3H, Ar-H).
231	IR: 1340, 1500 (NO_2), 2780, 2880 (C-H), 3200 (NH). NMR($CDCl_3$) 2.48 (t, 4H, N(CH_2)$_2$, J=5Hz), 3.47 (s, 2H, $CH_2C_6H_5$), 3.87 (t, 4H, CSN(CH_2)$_2$, J=5Hz), 7.18 (s, 5H, $CH_2C_6H_5$), 7.94 (s, 2H, Ar-H), 8.1 (s, 1H, Ar-H).
232	IR: 1300, 1500 (NO_2), 1590 (Arom), 2780, 2850, 2930 (C-H), 3050 (NH). NMR($CDCl_3$ + DMSO-d_6) 3.18 (t, 4H, N(CH_2)$_2$, J=5Hz), 4.04 (t, 4H, CSN(CH_2)$_2$, J=5Hz), 6.52-7.18 (m, 5H, Ar-H, N-C_6H_5), 7.46 (d, 1H, Ar-H, m to NO_2, J=9Hz), 7.88 (dd, 1H, Ar-H, p to chloro, J=3 & 9Hz), 8.03 (d, 1H, Ar-H, o to chloro, J=3Hz).
233	IR: 1345, 1545 (NO_2), 1610 (Arom), 2800-2900 (C-H), 3150 (NH). NMR($CDCl_3$) 2.35 (s, 3H, N-CH_3), 2.55 (t, 4H, N(CH_2)$_2$, J=5Hz), 4.1 (t, 4H, CSN(CH_2)$_2$, J=5Hz), 7.06-8.5 (m, 4H, Ar-H).
234	IR: 1310, 1500 (NO_2), 1600 (Arom), 2800 (C-H), 3310 (NH). NMR($CDCl_3$) 2.56 (t, 4H, N(CH_2)$_2$, J=5Hz), 3.6 (s, 2H, $CH_2C_6H_5$), 4.05 (t, 4H, CSN(CH_2)$_2$, J=5Hz), 7.3-8.5 (m, 9H, Ar-H).

1	2
235	IR: 1320, 1520 (NO_2), 1595 (Arom), 2780, 2860, 2950 (C-H), 3080 (NH). NMR($CDCl_3$) 3.54 (t, 4H, $N(C\underline{H}_2)_2$, J=5.5Hz), 4.22 (t, 4H, $CSN(C\underline{H}_2)_2$, J=5.5Hz), 6.82-8.68 (m, 9H, Ar-$\underline{H}$), 10.00 (hump, 1H, N$\underline{H}$, D_2O exchangeable).
237	IR: 1670 (CO), 2800-2900 (C-H), 3280 (NH). NMR($CDCl_3$ + DMSO-d_6) 2.0 (s, 3H, $COC\underline{H}_3$), 2.5 (t, 4H, $N(C\underline{H}_2)_2$, J=5Hz), 3.5 (s, 2H, $C\underline{H}_2C_6H_5$), 3.95 (t, 4H, $CSN(C\underline{H}_2)_2$, J=5Hz), 7.1-7.55 (m, 9H, Ar-$\underline{H}$).
238	IR: 1665, 1690 (CO), 2870, 2920, 2980 (C-H), 3300 (NH). NMR($CDCl_3$ + DMSO-d_6) 1.25 (t, 3H, $CH_2C\underline{H}_3$, J=7Hz), 2.08 (s, 3H, $COC\underline{H}_3$), 3.56 (t, 4H, $N(C\underline{H}_2)_2$, J=5Hz), 3.92 (t, 4H, $CSN(C\underline{H}_2)_2$, J=5Hz), 4.14 (q, 2H, $C\underline{H}_2$-CH_3, J=7Hz), 7.17 (d, 2H, Ar-$\underline{H}$, m to NHAc, J=9Hz), 7.53 (d, 2H, Ar-$\underline{H}$, o to NHAc, J=9Hz), 9.52 (hump, 1H, N$\underline{H}$, D_2O exchangeable).
240	IR: 1620 (Arom), 2780, 2880 (C-H), 3150, 3260 (NH_2). NMR($CDCl_3$) 2.52 (t, 4H, $N(C\underline{H}_2)_2$, J=5.5Hz), 3.54 (s, 2H, $C\underline{H}_2C_6H_5$), 3.88 (t, 4H, $CSN(C\underline{H}_2)_2$, J=5.5Hz), 6.54 (dd, 1H, Ar-$\underline{H}$, o to NH_2, J=2.5 & 9Hz), 6.68 (d, 1H, Ar-$\underline{H}$, o to chloro, J=2.5Hz), 7.24 (d, 1H, Ar-$\underline{H}$, m to chloro, J=6Hz), 9.3 (s, 5H, Ar-$\underline{H}$, $CH_2C_6\underline{H}_5$).

1	2
241	IR: 1590 (Arom), 2800, 2880 (C-H), 3150, 3250 (NH_2). NMR($CDCl_3$ + DMSO-d_6) 3.25 (t, 4H, $N(C\underline{H}_2)_2$, J=5.5Hz), 4.12 (t, 4H, $CSN(C\underline{H}_2)_2$, J=5.5Hz), 6.5-7.5 (m, 8H, Ar-$\underline{H}$), 8.3 (bs, 2H, $N\underline{H}_2$, D_2O exchangeable.
242	IR: 1600(Arom), 2820, 2900 (C-H), 3200-3320 (NH,NH_2). NMR(DMSO-d_6) 2.15 (s, 3H, N-$C\underline{H}_3$), 2.3 (t, 4H, $N(C\underline{H}_2)_2$, J=5Hz), 3.78 (t, 4H, $CSN(C\underline{H}_2)_2$, J=5Hz), 6.4 (d, 2H, Ar-$\underline{H}$, $\underline{o}$ to NH_2, J=9Hz), 6.78 (d, 2H, Ar-$\underline{H}$, $\underline{m}$ to NH_2, J=9Hz).
243	IR: 1600 (Arom), 2790, 2880 (C-H), 3100, 3280, 3350 (NH,NH_2). NMR($CDCl_3$) 2.35 (t, 4H, $N(C\underline{H}_2)_2$, J=5Hz), 3.4 (s, 2H, $C\underline{H}_2C_6H_5$), 3.68 (t, 4H, $CSN(C\underline{H}_2)_2$, J=5Hz), 6.45 (d, 2H, Ar-$\underline{H}$, $\underline{o}$ to NH_2, J=9Hz), 6.77 (d, 2H, Ar-$\underline{H}$, $\underline{m}$ to NH_2, J=9Hz), 7.15 (s, 5H, Ar-$\underline{H}$, $CH_2-C_6\underline{H}_5$).
244	IR: 1620 (Arom), 2800-2900 (C-H), 3200, 3300, 3380 (NH,NH_2). NMR(DMSO-d_6) 3.2 (t, 4H, $N(C\underline{H}_2)_2$, J=5Hz), 4.06 (t, 4H, $CSN(C\underline{H}_2)_2$, J=5Hz), 6.52 (d, 2H, Ar-$\underline{H}$, $\underline{o}$ to NH_2, J=9Hz), 6.72-7.24 (m, 7H, Ar-$\underline{H}$).
245	IR: 1640 (CO), 2060 (NCS), 2500-2680 (HCl salt), 2900 (C-H), 3220 (NH). NMR($CDCl_3$ + DMSO-d_6) 2.82 (s, 3H, $\overset{+}{N}C\underline{H}_3$), 3.25 (t, 4H, $\overset{+}{N}(C\underline{H}_2)_2$, J=5.5Hz), 4.0 (t, 4H, $CON(C\underline{H}_2)_2$, J=5.5Hz), 7.02-7.8 (m, 3H, Ar-$\underline{H}$), 8.2 (s, 1H, $N\underline{H}$, D_2O exchangeable).

1	2
246	IR: 1645 (CO), 2080 (NCS), 2400-2600 (HCl salt), 2870 (C-H), 3380 (NH). NMR($CDCl_3$) 3.25 (t, 4H, $N(C\underline{H}_2)_2$, J=5Hz), 4.1-4.4 (m, 6H, $CON(C\underline{H}_2)_2$ & $\overset{+}{N}-C\underline{H}_2C_6H_5$), 6.7-7.8 (m, 8H, Ar-H).
247	IR: 1640 (CO),2100 (NCS), 3360 (NH). NMR($CDCl_3$) 3.55 (t, 4H, $N(C\underline{H}_2)_2$, J=5Hz), 4.48 (t, 4H, $CON(C\underline{H}_2)_2$, J=5Hz), 6.8-7.8 (m, 8H, Ar-H).
248	IR: 1590 (Arom), 1630 (CO), 2100 (NCS), 2500-2660 (HCl salt), 2900 (C-H), 3250 (NH). NMR($CDCl_3$ + DMSO-d_6) 2.82 (s, 3H, $\overset{+}{N}-C\underline{H}_3$), 3.15-3.45 (m, 4H, $\overset{+}{N}-(C\underline{H}_2)_2$), 3.8-4.15 (m, 4H, $CON(C\underline{H}_2)_2$), 7.08 (d, 2H, Ar-H, J=9Hz), 7.64 (d, 2H, Ar-H, J=9Hz), 9.15 (s, 1H, NH, D_2O exchangeable).
249	IR: 1640 (CO), 2050 (NCS), 2400-2600 (HCl) 2870 (C-H), 3300 (NH). NMR($CDCl_3$) 2.70-4.10 (m, 4H, $N(C\underline{H}_2)_2$), 3.60-3.88 (m, 4H, $CON(C\underline{H}_2)_2$), 3.98 (s, 2H, $\overset{+}{N}C\underline{H}_2C_6H_5$), 6.9-7.55 (m, 9H, Ar-H), 8.84 (s, 1H, NH).

Table 5: Physical Data of Compounds



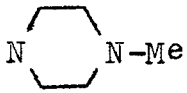
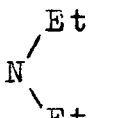
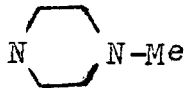
Compd. No.	R	X	m.p. °C	Yield %	Molecular formula (Mol.Wt.)		Analysis (%) Calcd.	Found
262		S	140	95	$C_{12}H_{16}N_2S$ (220)	C: H: N:	65.45 7.27 12.72	65.80 7.56 12.50
263		S	102-3	96	$C_{12}H_{17}N_3S$ (235)	C: H: N:	61.27 7.23 17.87	61.45 7.52 18.25
270		O	85	95	$C_{11}H_{16}N_2O$ (192)	C: H: N:	68.75 8.33 14.58	68.42 8.72 14.24
271		O	132	90	$C_{12}H_{16}N_2O$ (204)	C: H: N:	70.58 7.84 13.72	70.28 8.28 14.10
272		O	167-9	93	$C_{12}H_{17}N_3O$ (219)	C: H: N:	65.75 7.76 19.17	66.20 7.42 18.90

Table 5 - Spectral Data

Compd. No.	IR:KBr in cm^{-1}, NMR ppm (δ)
1	2
262	IR: 1590 (Arom), 2820, 2900, 3000 (C-H), 3200 (NH).
	NMR($CDCl_3$) 1.52 (s, 6H, $(C-CH_2)_3$), 3.64 (s, 4H, $N(CH_2)_2$), 6.9-7.2 (m, 5H, Ar-H).
263	IR: 1600 (Arom), 2800, 2920 (C-H), 3200 (NH).
	NMR($CDCl_3$) 2.18 (s, 3H, $N-CH_3$), 2.26 (t, 4H, $N(CH_2)_2$, J=5Hz), 3.66 (t, 4H, $CSN(CH_2)_2$, J=5Hz), 6.8-7.2 (m, 5H, Ar-H).
270	IR: 1600 (Arom), 1640 (CO), 2900-2980 (C-H), 3280 (NH).
	NMR($CDCl_3$) 1.02 (t, 6H, $2xCH_2CH_3$, J=7Hz), 3.2 (q, 4H, $2xCH_2CH_3$, J=7Hz), 6.8-7.32 (m, 5H, Ar-H).
271	IR: 1590 (Arom), 1620 (CO), 2820, 2900 (C-H), 3240 (NH).
	NMR($CDCl_3$) 1.5 (s, 6H, $(C-CH_2)_3$), 3.3 (s, 4H, $N(CH_2)_2$), 6.84-7.3 (m, 5H, Ar-H).
272	IR: 1600 (Arom), 1630 (CO), 2780, 2910 (C-H), 3260 (NH).
	NMR($CDCl_3$) 2.2 (s, 3H, $N-CH_3$), 2.28 (t, 4H, $N(CH_2)_2$, J=5Hz), 3.38 (t, 4H, $CON(CH_2)_2$, J=5Hz), 6.8-7.28 (m, 5H, Ar-H).

5. BIOLOGICAL ACTIVITY:

Most of the compounds were evaluated for their anthelmintic and antimicrobial activities in the Divisions of Parasitology and Fermentation Technology of this Institute.

5.1 Anthelmintic Testing:

5.11 Antihookworm Testing:

The compounds were tested for their antihookworm activity against experimental infections of Nippostrongylus brasiliensis in rats, Nematospiroides dubius in mice and Ancylostoma ceylanicum in hamsters by standard methods[60,61] with slight modifications[62] to suit local conditions.

Methodology:

Young male rats weighing 25-40 g (University of Freiburg strain) were inoculated subcutaneously or orally with 500 infective larvae of N.brasiliensis. Only those rats showing eggs in their stool on 8th day, were used for screening. An oral dose of the compound was given in a single or multiple dose on the day 9 post injection. The animals were starved over night prior to administration of drugs. This was done to ensure closure contact of the given chemotherapeutic agents with the parasites in absence of food material. Initially a single dose of 250 mg/kg of the compounds was used. The

compounds, insoluble in water, were made into fine suspension with tween 80. For each compound, 3 infected animals were used and a group of 3 animals was kept as untreated control. All the experimental and controlled rats were starved overnight before they were sacrificed on the day 3 post treatment. The total number of worms present in the intestine of a rat was counted on autopsy. The therapeutic efficacy of the compounds was assessed by comparing average number of the worms recovered from the treated group to that from the control group. If N is the average number of worms found in control group of animals and n is the average number of worms found in the treated group of animals, then the % deparasitization was calculated by the formula $\frac{N-n}{N} \times 100$.

A similar method was adopted when the screening was carried out against Nematospiroides dubius in mice and Ancylostoma ceylanicum in hamsters[63].

Results and discussion:

The compounds were initially tested for their antihookworm activity against Nematospiroides dubius in mice and Nippostrongylus brasiliensis in rats but none of them showed any noteworthy activity upto an oral dose of 250 mg/kg given for three days except 229 and 230 which showed 62-70% reduction of worms at dose of 250 mg/kg x 3 days. At a lower dose-schedule, compound 230 was found to

be effective in removing 60% of the worms at a dose of 100 mg/kg given orally for 3 days. The antihookworm testing of compounds carried out against Ancylostoma ceylanicum showed several compounds to possess high activity. Thus, compounds 62, 63, 72, 90, 110, 111, 127 and 168 cleared 100% of the A.ceylanicum worms from hamsters at an oral dose of 12.5-250 mg/kg given once or thrice daily for 3 days. The best compounds of the series are 110 and 168 which cleared 100% worms at a single oral dose of 12.5 mg/kg. Compounds 169 and 211 showed moderate activity and caused only 61.5 and 83.5% reduction in worm load at single oral dose of 250 mg/kg and 50 mg/kg respectively. Rest of the compounds were inactive upto 250 mg/kg given for 3 days. The anthelmintic testing results of the compounds are summarised in Table 6.

The antihookworm testing results would clearly indicate to the fact that a benzimidazole nucleus substituted with a 2-carbmethoxyamino function is an essential requirement for biological activity. This was evident from the fact that none of the benzthiazole derivatives of the type I, II showed any order of anthelmintic activity. However, the presence of a suitable pharmacophore at 5(6)-position of methyl benzimidazole-2-carbamate has a key role in altering (enhancement or lowering) of the biological activity. Thus, intmduction of a heterocyclic

Table 6: Efficacy of compounds against Ancylostoma ceylanicum infection in hamsters.

Compd. No.	Name	Dose mg/kg	% clearance of worms
62	2,2'-Dicarbomethoxyamino-5,5'-dibenzimidazolyl sulphide	50x1 25x1	100* 64-100
63	2,2'-Dicarbethoxyamino-5,5'-dibenzimidazolyl sulphide	100x3 50x3	100 90
72	2,2'-Dicarbethoxyamino-5,5'-dibenzimidazolyl sulphone	250x3 250x2	100 50-90
90	2,2'-Dicarbomethoxyamino-5,5'-dibenzimidazolylmethane	100x1 50x1	100 93.5
110	2,2'-Dicarbomethoxyamino-5,5'-dibenzimidazolyl oxide	25x1 12.5x1	100 94-100
111	2,2'-Dicarbethoxyamino-5,5'-dibenzimidazolyl oxide	50x1 25x1	100 77
127	Ethyl 5(6)-phenylbenzimidazole-2-carbamate	50x3 25x3	100 87-100
168	Methyl 5(6)-(4-isothiocyanatophenylthio)benzimidazole-2-carbamate	12.5x1	100
169	Ethyl 5(6)-(4-isothiocyanatophenylthio)benzimidazole-2-carbamate	250x1	61.5
211	1,2-Di-(4-isothiocyanatophenylsulfono)ethane	50x1	83.3

*All the experiments showing 100% clearance of worms by a particular compound, were repeated twice or thrice using 3 animals per experimental group and 3 were used as controls.

system such as a benzimidazole at the 5(6)-position of a benzimidazole ring gives rise to compounds devoid of any antihookworm or anticestode activity. Furthermore, incorporation of the benzimidazole ring in polynuclear heterocyclics such as I may generally lead to lowering or loss of activity. The best results are obtained when an appropriately substituted pharmacophore such as phenyl or benzimidazole ring are linked at the 5(6)-position of alkyl benzimidazole-2-carbamate via a heteroatom like sulphur or oxygen. Attempts to replace these heteroatoms by other groups like SO_2, CO, CH_2, S-CH_2-CH_2S-or piperazine in the dibenzimidazoles (III) leads to compounds having moderate to poor antinematode activity. The conclusions drawn from this study is in the close resemblance with the earlier studies describing the high anthelmintic activity and the molecular frame-work displayed by a series of benzimidazole anthelmintics 1-11.

5.12 Cestodicidal Testing:

The cestodicidal testing of all the compounds was carried out against experimental infection of Hymenolepis nana in rats using the technique of Steward[64] with slight modifications[65].

Methodology:

Newly weaned male rats of University of Freiburg strain were infected by feeding them with 200 viable ova

of H.nana. On day 15, after incubation of viable ova, rats which were found positive of H.nana ova in their stool were treated after being starved overnight. Initially a single oral dose of 250 mg/kg of the compound was given orally to 3 animals and 3 were kept as control. All the animals including controls were again starved overnight before being sacrificed on day 3 post treatment. The small intestine of individual animal was removed separately, washed and the worms collected and scored. Compounds removing 100% of the worms along with their scolices were considered active in this test.

Results and Discussions:

Most of the compounds were also tested for their anticestode activity against H.nana when some of the compounds showed high activity against the above tapeworms in rats and mice. Thus, compounds 62, 90, 91, 110, 111, 168, 169, 187 and 210 caused 100% elimination of worms along with their scolices from rats and mice at single oral dose of 30-250 mg/kg. Poor activity was shown by compound 172 which removed 50% of the worms at a single oral dose of 250 mg/kg from rats. The best compounds of the series are 62 which cleared 100% of H.nana worms from rats at single oral dose of 70 mg/kg and 168 which caused 100% reduction in worm load at a single oral dose of 30 mg/kg. However, 62 and 168 eliminated 100 and 80%

worms respectively from mice at single oral dose of 100 mg/kg. Praziquantel was used as standard drug which removed 100% of the H.nana worms along with scolices at a single dose of 5 mg/kg given orally. Rest of the compounds were found to be inactive upto an oral dose of 250x3 mg/kg. The detail results of the cestodicidal activity is summarized in Table 7.

The fact, that a number of benzimidazole anthelmintics such as mebendazole and fenbendazole exhibit marked activity against different cestodes, led us to evaluate their cestodicidal activity against a common human tapeworm, H.nana (dwarf tapeworm). The testing results showed that the structural parameters required for biological activity in methyl benzimidazole-2-carbamates is complementary to those needed for antihookworm activity described in Sec.5.11.

5.2 Antimicrobial Activity:

Most of the compounds were also evaluated for their in vitro growth inhibitory activity against different strains of bacteria and fungi and results are summarized in Table 8. The bacteria and fungi were maintained on nutrient and Sabouraud's agar slants[66] respectively and testing was done using the two fold serial dilution technique by dissolving the compounds in ethanol. The bacteria used were Staphylococcus aureus (gram positive,

Table 7: Efficacy of compounds against Hymenolepis nana infections in rats.

Compd. No.	Name	Dose mg/kg	% clearance of worms
62	2,2'-Dicarbomethoxyamino-5,5'-dibenzimidazolyl sulphide	70x1 100x1 50x1	100 100[a] 60[a]
90	2,2'-Dicarbomethoxyamino-5,5'-dibenzimidazolylmethane	250x1	100
91	2,2'-Dicarbethoxyamino-5,5'-dibenzimidazolylmethane	250x1 100x1	100 50
110	2,2'-Dicarbomethoxyamino-5,5'-dibenzimidazolyl oxide	250x1 100x1 50x1	100 60 66
111	2,2'-Dicarbethoxyamino-5,5'-dibenzimidazolyl oxide	250x1 100x1	100 60
168	Methyl 5(6)-(4-isothiocyanatophenylthio)benzimidazole-2-carbamate	30x1 100x1 50x1	100 80[a] 55.5[a]
169	Ethyl 5(6)-(4-isothiocyanatophenylthio)benzimidazole-2-carbamate	250x1 100x1 50x1 25x1	100 100 33 33
172	Methyl 5(6)-(4-isothiocyanatophenylsulfono)benzimidazole-2-carbamate	250x1	50
187	Ethyl 5(6)-(4-isothiocyanatophenoxy)benzimidazole-2-carbamate	250x1	100
210	1,2-Di-(4-isothiocyanatophenylthio)ethane	250x1	100

a, in mice.

resistant to 2500 units of penicillin/ml), Streptococcus faecalis, Salmonella typhi (gram negative), Escherichia coli, Agrobacterium tumefaciens, Klebsiella pneumoniae, Pseudomonas aeruginosa and Proteus vulgaris, while the fungi used were Candida albicans, Trichophyton mentagrophytes, Cryptococcus neoformans, Microsporum canis, Aspergillus niger, Aspergillus fumigatus and Sporotrichum schenckii. Tetracycline and amphotericin B were used as standard drugs in antibacterial and antifungal testings respectively.

5.21 Antibacterial Assay:

All the bacteria were maintained on nutrient agar slants[66]. Testing was done in nutrient broth. After inoculation with a loopful of culture from the slant, the seeded broth were incubated at 37±1°C for 24 hr. The two fold serial dilution technique[67] was applied. A set of tubes containing only inoculated broth was kept as controls. After incubation for 24 hr, the last tube with no growth of the microorganism was taken to represent the minimum inhibitory concentration (MIC, expressed in µg/ml). A compound inhibiting the growth of microbe in a concentration of 25 µg/ml was considered to be active.

5.22 Antifungal Assay:

All the fungi were maintained on Sabouraud's agar slants and the compounds were tested in Sabouraud's broth. Loopfuls of the fungal culture (C.albicans and

C.neoformans) from the slants were inoculated into the broth and the respective inoculated broths were used for testing after incubation for 24 hr at 28±1°C. In the case of small fungi, small pieces of mycelia were introduced into conical flask containing 50 ml of the broth. The flasks were then incubated with shaking for 24-48 hr and the clear broths were taken out of the flasks. The compounds were tested by serial dilution technique as described in antibacterial assay. The compounds which inhibited the growth of fungus at 25 µg/ml concentration, was considered to be active.

5.23 Results:

The compounds were tested against various strains of bacteria and found to be inactive except 215 which inhibited the growth of Streptococcus faecalis and Klebsiella pneumoniae at minimum inhibitory concentrations (MIC) of 25 and 25 µg/ml and 242 which inhibited the growth of above microbes at MIC's of 25 and 50 µg/ml respectively. The growth of rest of the strains remained unaffected by either of the compounds tested.

In antifungal testing the best compound of the series was 214 which inhibited the growth of all the fungi used at the MIC's of 3.125-12.5 µg/ml. However, 215 caused the inhibition of C.albicans ,T.mentagrophytes and A.fumigatus at MIC's of 6.25, 6.25 and 100 µg/ml. Rest of the compounds inhibited the growth at higher concentrations and results are summarized in Table 8.

Table 8: In vitro antifungal activity of the compounds

Compd. No.	Minimum inhibitory concentration (MIC) in µg/ml				
	C. albicans	C. neoformans	S. schenckii	T. mentagrophytes	A. fumigatus
130	>100	>100	>100	100	>100
131	>100	>100	>100	100	>100
133	>100	50	>100	100	>100
134	100	50	100	50	50
145	>100	>100	>100	100	>100
214	3.125	3.125	3.125	3.125	12.5
215	6.25	>100	>100	6.25	100
220	25	100	100	>100	>100
221	25	100	100	>100	>100
222	100	>100	>100	100	100
225	100	>100	>100	50	50
232	25	25	50	>100	>100
241	50	50	25	25	>100
244	>100	100	>100	100	100
245	100	50	25	25	>100

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S U M M A R Y

The survey of world-wide incidence of various helminth infestations in man which appeared time to time reveals that despite several measures taken to eradicate helminth infections its growing trend has not been checked[1]. Although helminth infections are not generally fatal, they contribute to the major public health problems in tropical and subtropical regions of the world[2,3] and may also lead to several clinical complications causing even death of the patient in absence of immediate medical care. The high prevalence of helminth infections is partly due to the poor sanitary habits and lack of prophylaxis followed by masses, abundance of proper natural conditions for the developments of helminth juveniles and partly due to the lack of suitable drugs available for the treatment of different forms of helminthiasis. The present thesis is an effort to develop ideal chemotherapeutic agents for the treatment of infections due to hookworms and cestodes, the two major helminth diseases of tropics.

The efforts to substitute classical anthelmintics by more effective and safer drugs was unsuccessful till 1961 when Merck came out with the discovery of thiabendazole[4], a new class of anthelmintic possessing broad spectrum of activity against a variety of nematode parasites in man and domestic animals. This led to the discovery of a series

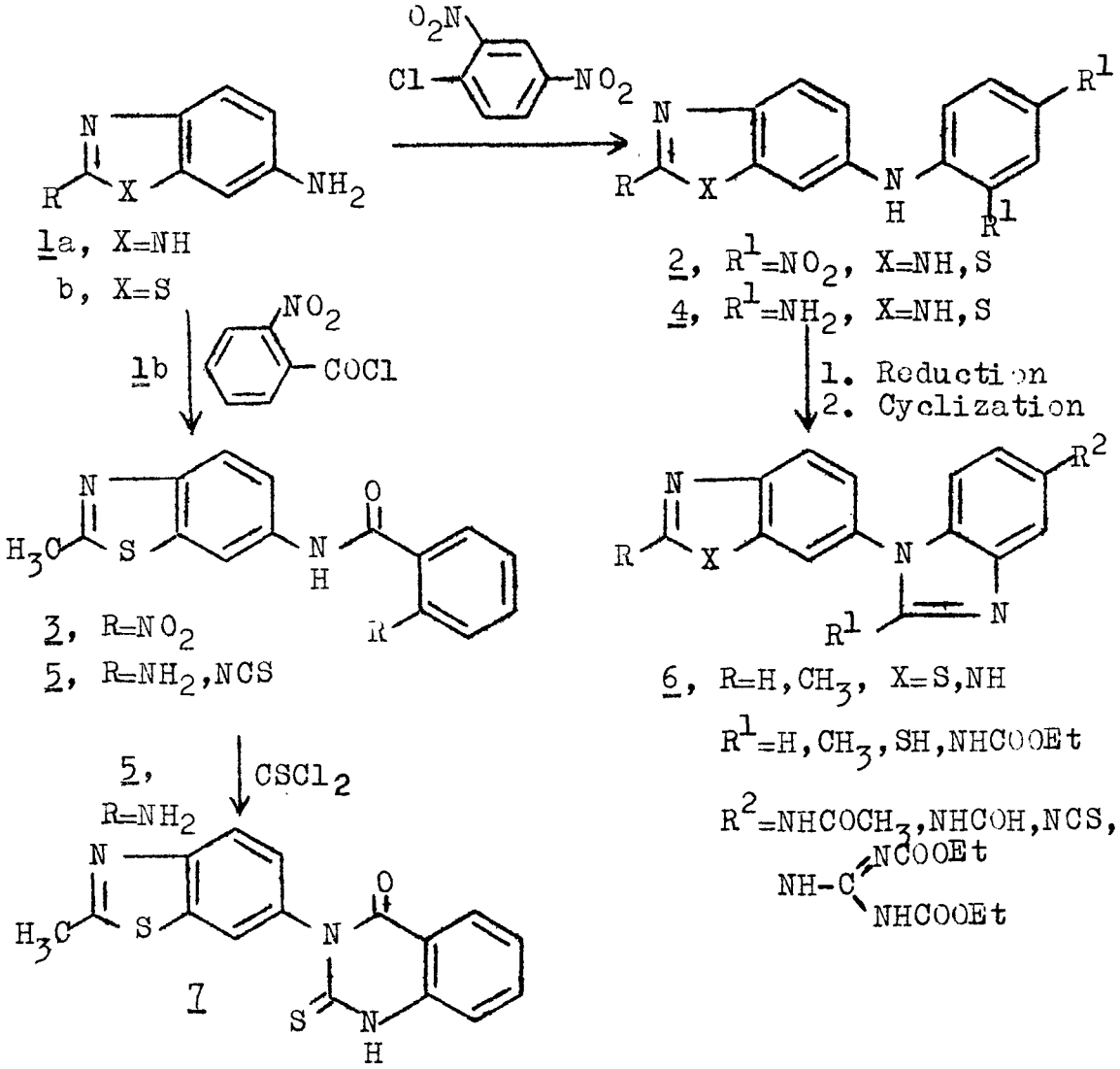
of potent benzimidazole anthelmintics of which mebendazole[4] and fenbendazole[4] showed high promise in curing nematode and cestode infestations and also established benzimidazole heterocycle as a useful pharmacophore for building molecules with broad spectrum of antiparasitic activity.

The first chapter of the thesis presents a review dealing with the recent developments in the treatment of hookworm and cestode infections. The second chapter comprises of the synthesis and biological activity of the different classes of the compounds based on the powerful anthelmintic activity associated with benzimidazoles[5], diaryl sulfides and sulfones[6] and bitoscanate[7]. This study has been carried out with a view to develop better anthelmintics as also to delineate minimal structural requirements for optimal anthelmintic activity in the molecular frame-work exhibited by the 'lead' molecules.

Synthesis of 5(6)-N-heteroarylbenzimidazoles and benzthiazoles

Several 5(6)-(1-benzimidazolyl)benzimidazoles and 6-(1-benzimidazolyl)benzthiazoles (6) have been prepared starting with the condensation of 5(6)-aminobenzimidazoles (1a) and 6-aminobenzthiazoles (1b) with 2,4-dinitrochlorobenzene or 2-nitrobenzoylchloride to give 5(6)-(2,4-dinitrophenyl)aminobenzimidazoles and benzthiazoles (2)

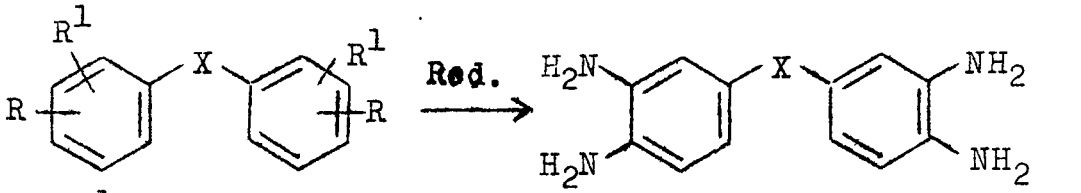
and 6-(2-nitrobenzoyl)aminobenzthiazole (3) respectively. Reduction of 2 and 3 with Raney-nickel and H_2 or hydrazine-hydrate and Raney-nickel gave the corresponding amines (4 and 5) which were cyclized with different cyclizing agents to give the title products (6 and 7)[8,9].



Synthesis of 2,2'-disubstituted-5,5'-dibenzimidazolyl derivatives

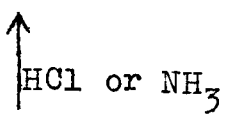
Based on the powerful anthelmintic activity associated with benzimidazoles[5], several 2,2'-disubstituted-5,5'-dibenzimidazolyl derivatives (11) have been prepared in order to study the role of benzimidazole moiety as a

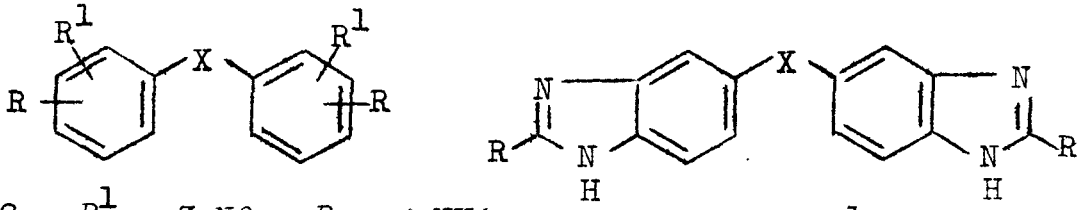
carrier molecule. The key intermediates in the synthesis of above compounds were 3,3'-dinitro (or diamino)-4,4'-diamino (or dinitro)diphenyl derivatives (9) obtained either by hydrolysis of 4,4'-diacetamido-3,3'-dinitro diphenyl derivatives (8a) or by amination of 4,4'-dichloro-3,3'-dinitrodiphenyl derivatives (8b) or by direct reaction of 5-chloro-2-nitroacetanilide with sodium sulfide. Reduction of 8 with hydrazine-hydrate and Raney-nickel, Raney-nickel and H_2 or ferrous sulphate-ammonia gave the corresponding 3,3',4,4'-tetra-aminodiphenyl derivatives (10). Reaction of 10 with 1,3-dicarbalkoxy-S-methylisothioureas, acetic acid or formic acid yielded the title compounds 11.



9, R^1 = 3-NH_2 or 3-NO_2
R = 4-NH_2 or 4-NO_2

10



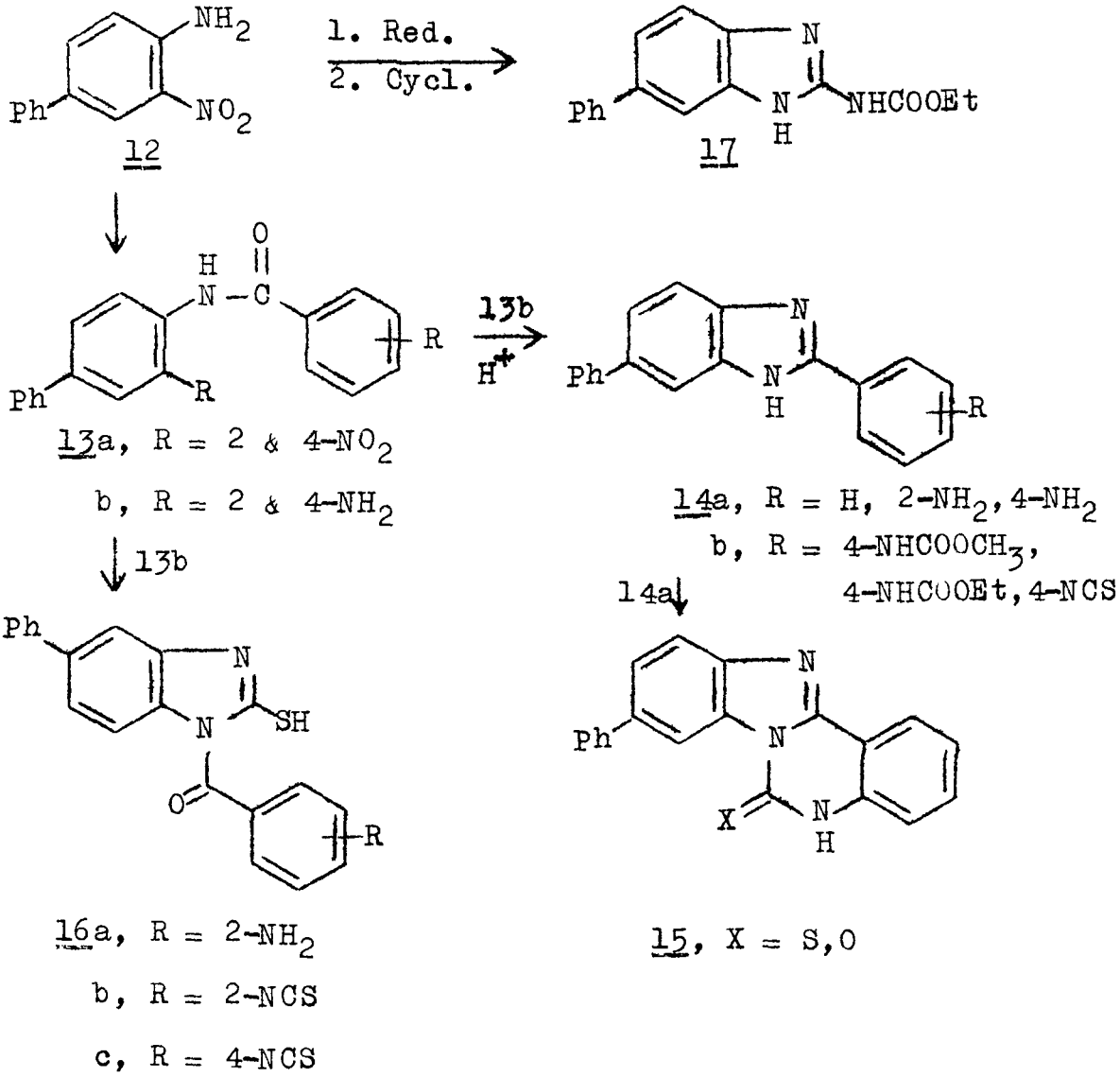


8a, R^1 = 3-NO_2, R = 4-NHAc
b, R^1 = 3-NO_2, R = 4-Cl

11, R = $NHCOOR^1$, H, CH_3
R^1 = CH_3, C_2H_5
X = S, SO_2, CO, CH_2, O
$S(CH_2)_2S$, CON⟨⟩NCO

Synthesis of 2,5-diarylbenzimidazoles and their cyclic analogs

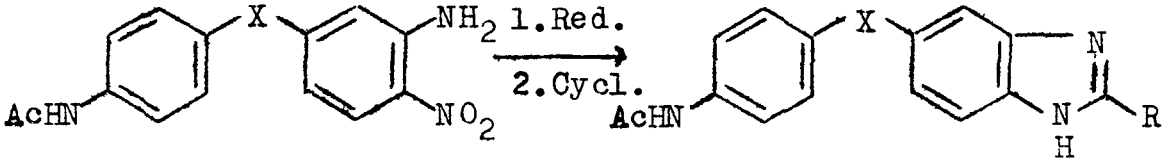
Synthesis of 2,5-diarylbenzimidazoles was undertaken based on the activity of several 2-arylbenzimidazoles. 4-Amino-3-nitrobiphenyl (12), on reaction with nitrobenzoyl chlorides, gave 4-(aroyl)amino-3-nitrobiphenyls (13a) which were reduced with hydrazine-hydrate and Raney-nickel to yield the corresponding amines 13b. Cyclization of 13b with acid gave 2,5-diarylbenzimidazoles (14a). Reaction of 2-(4-aminophenyl)-5(6)-phenylbenzimidazole (14a, R= 4-NH_2) with alkyl chloroformates and thiophosgene yielded 2-(4-carbalkoxyaminophenyl and 4-isothiocyanatophenyl)-5(6)-phenylbenzimidazoles (14b). Similar reaction of 14a (R = 2-NH_2) with alkyl chloroformates and potassium ethyl xanthate yielded the cyclic products 15 while the reaction of 13b with thiophosgene yielded 1-(2-amino, 2-isothiocyanato and 4-isothiocyanatobenzoyl)-2-mercapto-5-phenylbenzimidazoles (16a-c). 4-Amino-3-nitrobiphenyl (12) was also used to prepare ethyl 5(6)-phenylbenzimidazole-2-carbamate (17) by reduction followed by cyclisation of the resulting amine with 1,3-dicarbethoxy-S-methylisothiourea[10].



2-Substituted-5(6)-(4-substituted phenoxy, phenylthio and sulfono)benzimidazoles

5-(4-Acetamidophenoxy and phenylthio)-2-nitroanilines (18) were used to prepare several benzimidazoles of the type 21. Reduction of 18 with hydrazine-hydrate and Raney-nickel and subsequent cyclization with formic acid, acetic acid and 1,3-dicarbalkoxy-S-methylisothioureas gave

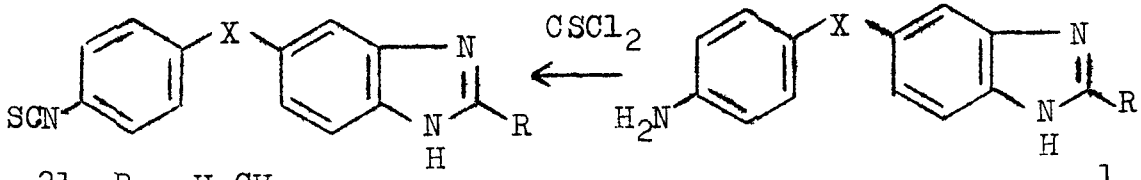
the corresponding 2,5(6)-disubstituted benzimidazoles (19). Oxidation of 19 (X=S) with $KMnO_4$-CH_3COOH gave the sulfones 19 (X=SO_2). Acid hydrolysis of 19 with 10% HCl gave the corresponding amines (20) which were treated with thiophosgene to give 2-substituted-5(6)-(4-isothiocyanatophenoxy, phenylthio and sulfono)benzimidazoles (21).



18, X = O,S

19, R = H, CH_3, $NHCOOR^1$
R^1= CH_3, C_2H_5
X = O,S,SO_2

$\downarrow H^+$



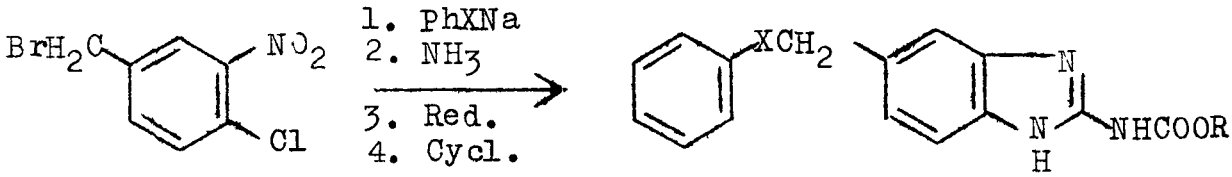
21, R = H,CH_3, $NHCOOR^1$
R^1= CH_3,C_2H_5
X = O,S,SO_2

20, R = H, CH_3, $NHCOOR^1$
R^1= CH_3, C_2H_5
X = O, S, SO_2

Synthesis of 5(6)-thiophenoxymethyl and phenoxymethyl benzimidazole-2-carbamates

The higher homologue (23) of fenbendazole was synthesized starting from 4-chloro-3-nitrobenzyl bromide (22) by the sequence of reactions described below. This has helped in evaluating the effect of introduction of one

methylene unit at 5(6)-position of benzimidazole on biological activity of fenbendazole.

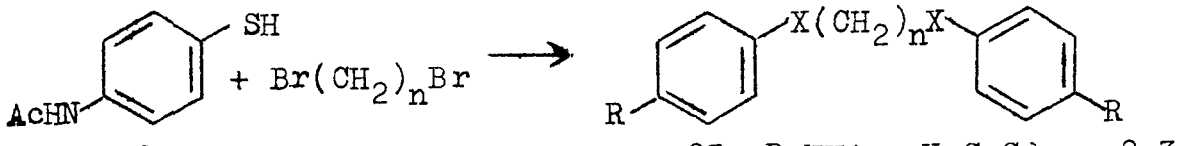


22

23, X = O, S, R = CH_3, C_2H_5

Synthesis of 1,2 and 1,3-disubstituted alkanes and 1,4-disubstituted piperazines

In order to study the change in biological activity of 4,4'-diisothiocyanatodiphenyl sulfide and sulfone by increasing the distance between two aryl functions by introduction of 2 or 3 CH_2 units, synthesis of 1,3- and 1,2-disubstituted alkanes (27) was undertaken. 4-Acetamidothiophenol (24), on reaction with 1,2-dibromoethane and 1,3-dibromopropane, yielded 1,2 and 1,3-di-(4-acetamidophenylthio)alkanes (25). Oxidation of 25 with $KMnO_4$-CH_3COOH gave the corresponding sulfones 25 ($X=SO_2$) which were hydrolysed in presence of acid to give the desired amines 26. Reaction of 26 with thiophosgene yielded the title compounds 27.



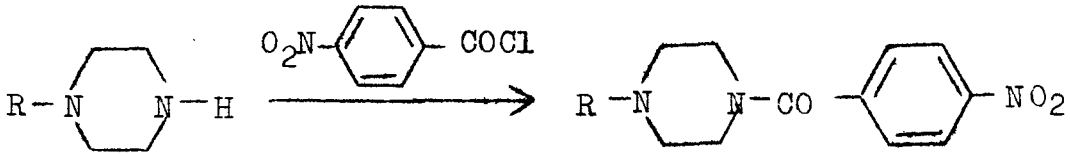
24

25, R=NHAc, X=S, SO_2, n=2,3

26, R=NH_2, X=S, SO_2, n=2,3

27, R=NCS, X=S, SO_2, n=2,3

The synthesis of compounds of the type 30 obtained by replacement of thio and sulfono linkage of 4,4'-diisothiocyanatodiphenyl sulfide and sulfone by piperazine moiety, a more active pharmacophore for antinematode activity, was also carried out. The synthesis starts with the reaction of either anhydrous piperazine or 4-nitrophenylpiperazine (28) with 4-nitrobenzoyl chloride to give 1,4-disubstituted piperazines (29). Reduction of 29 gave the corresponding diamines which were converted to isothiocyanates (30) by treating with thiophosgene.

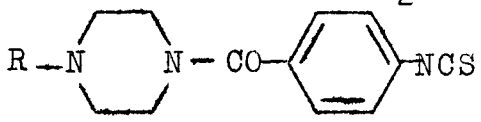


28, R=H, 4-nitrophenyl

29, R=4-nitrophenyl

R=4-nitrobenzoyl

↓ 1. Red.
2. $CSCl_2$



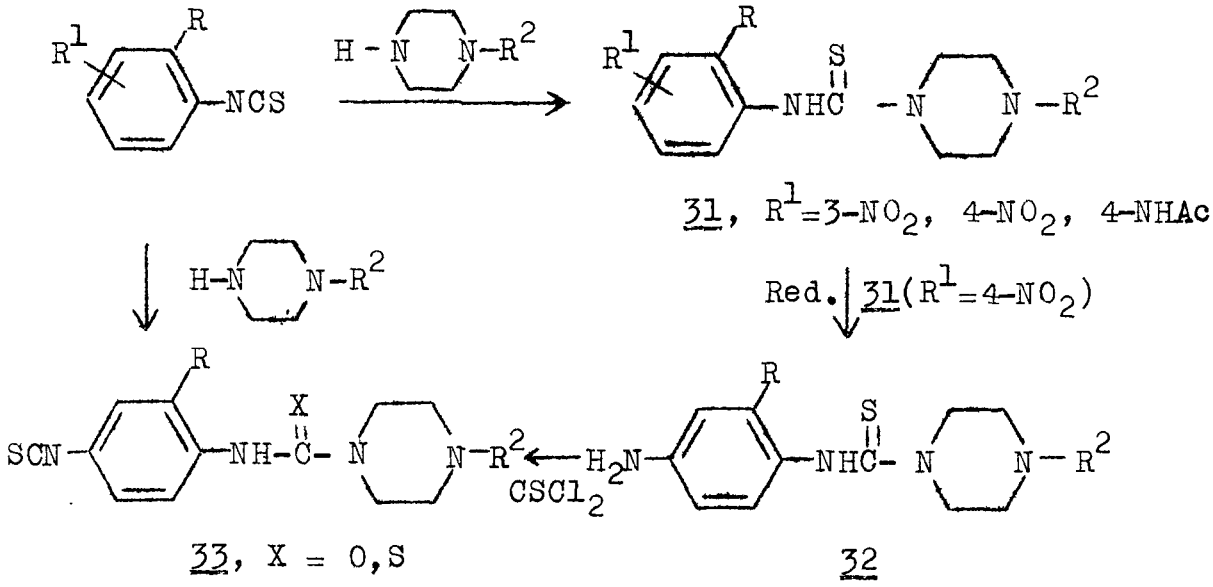
30, R=4-isothiocyanatophenyl

R=4-isothiocyanatobenzoyl

Synthesis of substituted thiocarboxamides, carboxamides and thioureas

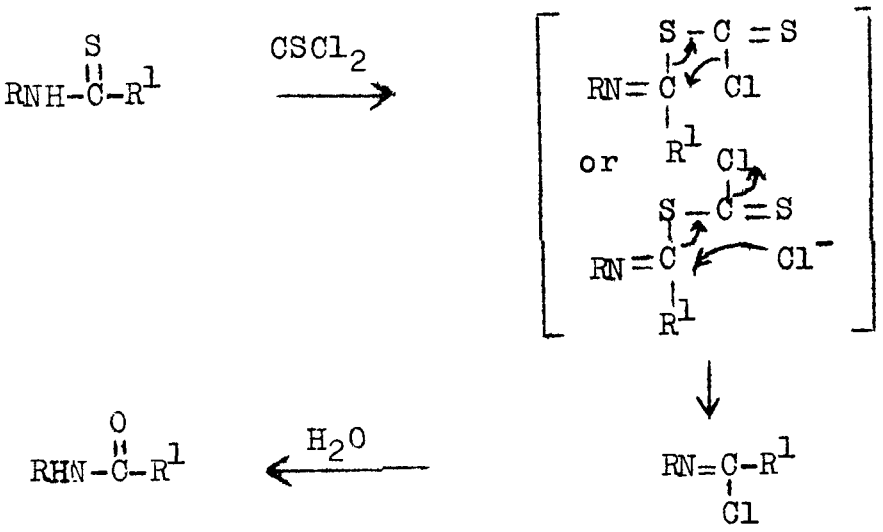
Several substituted thiocarboxamides, and carboxamides have been preparod as structural analog of bitoscanate. Reaction of different piperazines and anilines with

various phenylisothiocyanates gave the thiocarboxamides (31) which were reduced to the corresponding amines (32). Conversion of 32 into isothiocyanates by reacting with thiophosgene resulted in an unusual desulphurization of thiocarboxamides to give carboxamides (33, X=O). Thiocarboxamides (33, X=S) carrying the isothiocyanato function were conveniently prepared by reaction of one mole of piperazines with p-phenylenediisothiocyanate (bitoscanate). Several thioureas were also prepared either by reaction of 2-aminobenzimidazole or 4-aminoacetanilide on substituted phenylisothiocyanates[11].



The unusual desulphurization of thiocarboxamides and thioureas with thiophosgene was studied by converting a number of thiocarboxamides, thioureas and thiamide to their corresponding oxygen analogs with the help of

thiophosgene and possible mechanism for desulphurization has been proposed[12].



Biological Activity:

Most of the compounds have been evaluated for their anthelmintic activity against Nippostrongylus brasiliensis in rats, Nematospiroides dubius in mice, Ancylostoma ceylanicum in hamsters and Hymenolepis nana in rats and mice. A large number of 2,5-disubstituted benzimidazole derivatives showed promising antihookworm and anticestode activity which is reported in the thesis. The best compounds of this study were found to be 2,2'-dicarbomethoxyamino-5,5'-dibenzimidazolyl oxide (11, X=O, R=NHCOOCH$_3$) and sulphide (11, X=S, R=NHCOOCH$_3$) which exhibited 100% removal of A.ceylanicum at a single oral dose of 12.5-25 mg/kg in hamster while 100% of the H.nana worms were expelled by 2,2'-dicarbomethoxyamino-5,5'-dibenzimidazolyl sulfide (11, X=S, R=NHCOOCH$_3$) and

methyl 5(6)-(4-isothiocyanatophenylthio)benzimidazole-2-carbamate (21, X=S, R=$NHCOOCH_3$) at single oral doses of 70 and 30 mg/kg respectively from rats. Compound 11 (X=O, R=$NHCOOCH_3$) was 100% effective in causing complete eradication of H.nana from rats at a single oral dose of 250 mg/kg. The results of the in vitro antimicrobial activity of some of the compounds are also reported in the thesis.

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1. A new convenient method of desulphurization of thioureas and thioamides, S.Abuzar, S.Sharma and R.N. Iyer, Indian J. Chem., 19B, 211 (1980).

2. Synthesis of N-aryl and N-heteroarylbenzimidazoles as potential anthelmintics, S.Abuzar, S.Sharma and R.N.Iyer, Indian J. Chem., 19B, 599 (1980).

3. Synthesis of 6-N-aryl and heteroarylbenzthiazoles as potential anthelmintics, S.Abuzar and S.Sharma, Z. Naturforsch., 36b, 108 (1981).

4. Synthesis of substituted thiocarboxamides, carboxamides and thioureas as potential anthelmintic and antimicrobial agents, S.Abuzar and S.Sharma, Indian J. Chem.,20B, 230 (1981).

5. Synthesis of substituted benzimidazoles as potential anthelmintics, S.Abuzar and S.Sharma, Arch. Pharm. (in press).

6. The benzimidazole anthelmintics - Chemistry and biological activity, S.Sharma and S.Abuzar, Prog. Drug Res., Birkhäuser Verlag, Basel, Edited by E.Jucker, (in press).

7. A process for the synthesis of anthelmintic 2,2'-dicarbalkoxyamino-5,5'-dibenzimidazolyl derivatives, S.Abuzar, S.Sharma, J.C.Katiyar, P.K.S.Visen, S.Ram and A.B.Sen, Indian Pat. Appln., No.379/Del/81 dated 12.6.1981

8. A process for the synthesis of anthelmintic 2,2'-dicarbalkoxyamino-5,5'-dibenzimidazolyl oxides, S.Abuzar, S.Sharma, J.C.Katiyar, S.M.Johri, S.Gupta, S.Ram and A.B.Sen, Indian Pat. Appln. pending.

9. A process for the synthesis of anthelmintic alkyl 5(6)-(isothiocyanatophenylthio and sulfono)benzimidazole-2-carbamates, S.Abuzar, S.Sharma, S.M.Johri, S.Gupta, S.Ram, J.C.Katiyar and A.B.Sen, Indian Pat. Appln. pending.